BoxInterferences@uspto.gov
Telephone: 571-272-4683

Paper 417
Entered: 6 August 2009

UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Interference 105,592 McK
Technology Center 1600

CENTOCOR, INC.
(Inventors: Jill Giles-Komar *et al.*)

Application 10/912,994,
Junior Party,

v.

ABBOTT GmbH & CO., KG,
(Inventors: Jochen Salfeld *et al.*)

Patent 6,914,128,
Senior Party,

Before: FRED E. McKELVEY, *Senior Administrative Patent Judge*, and RICHARD E. SCHAFER and SALLY GARDNER LANE, *Administrative Patent Judges*.

McKELVEY, *Senior Administrative Patent Judge*.

MEMORANDUM OPINION
Final decision—Decision on Abbott Motion 7

A. Introduction

The interference is before a merits panel for consideration of priority and other issues.

B. Abbott Motion 7 will be considered first

Junior party

Centocor is the "Junior Party" and therefore bears the ultimate burden on the issue of priority. 37 C.F.R. § 41.207 (2008), first sentence.

Priority statements

In its priority statement, Centocor alleges a corroborated conception date no later than 18 February 1997. Paper 33, page 2.

Centocor alleges a corroborated actual reduction to practice no later than 23 June 1997. Paper 33, page 2.

In its priority statement, Abbott alleges an earlier corroborated conception no later 16 July 1993. Paper 40, second page.

Abbott alleges an earlier corroborated actual reduction to practice no later than 5 June 1995. Paper 40, second page.

Centocor motion for judgment based on priority

Centocor filed Centocor Motion 3 (Paper 154) for judgment based on priority in which Centocor alleges that it actually reduced to practice consistent with its priority statement.

Abbott filed Abbott Opposition 3 (Paper 193) and maintains that Centocor did not carry its burden of proof.

Abbott motion for judgment based on priority

Contingent on Centocor having not carried its burden, Abbott nevertheless filed Abbott Motion 7 (Paper 188) alleging, *inter alia*, that Abbott conceived and actually reduced to practice *before* the earliest day which Centocor is permitted to prove, i.e., 23 June 1997.

Centocor has opposed. Paper 194.

Abbott has replied. Paper 238.

Board will consider Abbott's priority motion first

The Board is authorized to take up motions in any order. 37 C.F.R. § 41.125(a) (2008).

We elect to consider first Abbott Motion 7.

If Abbott prevails on Abbott Motion 7, the issue of priority is resolved in favor of Abbott and against Centocor.

C. The count and its interpretation

The count consists of two alternative embodiments: (1) a Centocor embodiment and (2) an Abbott embodiment.

The count reads:

Count 1

An isolated human antibody according to claim 1 of [Centocor] application 10/912,994 or claim 1 of [Abbott] U.S. Patent, 6,914,128.

Centocor claim 1 (Paper 5)

An isolated human antibody, or an antigen-binding portion thereof, that binds to human IL-12, wherein said human antibody is a neutralizing antibody.

Abbott claim 1 (Paper 9)

An isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a K_d of 1×10^{-10} M or less and a k_{off} rate constant of $1 \times 10^{-3} s^{-1}$ or less, as determined by surface plasmon resonance.

Abbott has elected to present its proofs in terms of the Centocor embodiment. The meaning of terms in the Centocor embodiment will be determined based on the Centocor specification. 37 C.F.R. § 41.200(b) (2008).

D. Abbott Motion 7

1. Abbreviations

The following abbreviations are used in this opinion.

AV	Amy Venturini—when used in GI documents
AW	Angela Widom--when used in GI documents
BASF	BASF Bioresearch Corporation
CAT	Cambridge Antibody Technology
CM	COS conditioned media
COS cells	African Green Monkey kidney cells (Ex 2069, page 43:25 to page 44:3)
CPA	Counts per million
ELISA	Enzyme-Linked ImmunoSorbent Assay
FDA	Food and Drug Administration
GI	Genetics Institute
inh	Inhibition
"Joe"	Name given by BASF to antibodies. Each antibody was named Joe and was given a Joe number, e.g., Joe 7.
MBGE group	A group of scientist working at GI working with Geertruida Veldman
mg/ml	Micrograms per microliter
OD	Optical density.
PBMC	Peripheral blood mononuclear cells
PHA	Phytohemagglutinin
PHA Assay	PHA Blast Proliferation assay

Project	A BASF, GI and CAT collaboration project known as "Isolation of Human Antibodies which Neutralize Human IL-12."
RBA	Receptor binding assays
scFv	Functional antigen binding portions of human antibodies, one example of which would be Joe 7. As explained by White during cross, "sc" means single chain and "Fv" means fragment. Ex 2069, page 12:11-21. See also Ex 2071, page 14:10-13 (Vaughan cross)
SPR	Surface plasmon resonance
TV	When used in GI documents means Geertruida ["Trudi"] Veldman

2. Involved entities and individuals

The invention was developed as a result of a collaborative effort of at least three entities and numerous individuals within those entities.

The entities are:

1. Abbott Bioresearch Corporation, formerly BASF Bioresearch Corporation (**BASF**).

2. Cambridge Antibody Technology (**CAT**), now MedImmune Ltd.

3. Genetics Institute (**GI**), now an affiliate of Wyeth.

The individuals are the following.

The reader should be aware that BASF was located in Cambridge, MA while CAT was located in Cambridge, UK.

Name	Company	Inventor	Testimony Exhibit Number
Banerjee, Subhashis M.D.	BASF Consultant	Yes	1320
Carreno, Beatriz Ph.D.	GI		1332
Duncan, Alexander R. Ph.D.	CAT	Yes	1324 2066
Elvin, John Ph.D.	CAT	Yes	1323 2067
Ghayur, Tariq Ph.D.	BASF		1322
Gimlich, Robert	GI		1335
Hayden-Jackson, Brenda	MedImmune		1337
Kamen, Robert Ph.D	BASF		1321 1321 Rev 2068
Maguire, Phil	Wyeth		1338
Moitoso, Jennifer	Wyeth		1333
Murtha-Riel, Patricia (deceased)	BASF		
O'Brien, Gayle	Abbott		1336
Roguska, Michael Ph.D.	BASF	Yes	
Salfeld, Jochen Ph.D.	BASF	Yes	1318
Tracey, Daniel Ph.D.	BASF	Yes	1319
Tomkinson, Kathy	GI		1331
Vaughan, Tristan Ph.D.	CAT		1326 2071

Veldman, Geertruida M. Ph.D.	GI	Yes	1327 1327 Rev 2070
Venturini, Amy	GI	Yes	1328
White, Michael Ph.D.	BASF	Yes	1340 2069
Widom, Angela	BASF	Yes	1329
Wilton, Jane	CAT		1325 2073
Wong, Winnie Ph.D.	CAT		
Wood, Nancy	GI		1330

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2 3. List of graphs reproduced in opinion

3

Graph Number in Opinion	Exhibit Number from which Graph was reproduced	Scientist followed by Description
1	1344	Widom: AW 48 RB Assay Test ScFv Joe #7
2	1344	Widom: AW 48 RB Assay Test ScFv Joe #10
3	1346	Widom: AW 74 RB Assay: Test Joe#20 (Lot#1108)
4	1346	Widom: AW 74 RB Assay: Test Joe#22 (Lot#1108)
5	1350	Venturini: AV 64 PHA Blast Assay ScFv Inhibition of hIL-12

6	1342	Veldman: TV 1632 PHA Blast Assay Joe7: scFv and Full AB +/- human IgG
7	1342	Veldman: TV 1632 PHA Blast Assay Joe10: scFv and Full Ab =/- human IgG
8	1343	Veldman: TV 1646 PHA Blast Assay Compare scFv Joe7 and JDes9
9	1353	Venturini: AV 83 PHA Blast Assay
10	1353	Venturini: AV 83 PHA Blast Assay Compare ScFv to full length Ab
11	1345	Widom: Eight graphs including (1) AW 51 RB Assay Test ScFv Joe #7 Lot# 0921; (2) AW 51 RB Assay Test ScFv Joe #10 Lot# 0921and (3) AW 51 RB Assay Test ScFv Joe #10 Lot# 0831
12	1346	Widom: AW 74 RB Assay: Joe#7 (Lot#0921)
13	1347	Widom: AW 115 RB Assay: Test JDes9
14	1347	Widom: AW 112 RB Assay: Test Joe#20
15	1351	Venturini: AV 66 PHA Blast Assay ScFv Inhibition of hIL-12
16	1352	Venturini: AV 80 PHA Blast Assay Compare ScFv to full length Ab

17	1352	Venturini: AV 80 PHA Blast Assay Compare ScFc to full length Ab
18	1354	Venturini: AV 89 PHA Blast Assay Compare ScFc to full length Ab =/- HIgG
19	1355	Venturini: AV 120 PHA Blast Assay Compare ScFv Jdes9 with full antibody Joe 9g1

4. Findings of fact

The following findings of fact are supported by a preponderance of the evidence.

To the extent that a finding of fact is a conclusion of law, it may be treated as such.

A reference to "Abbott Fact x" is a reference to the facts as set out in Abbott Reply 7 (Paper 238), beginning at page 14. For example, Abbott Fact 1 refers to Abbott Fact 1 as set out in Paper 238, page 14.

A reference to "Centocor response to Abbott Fact x" is a reference to a Centocor response to an Abbott Fact. For example, "Centocor response to Abbott Fact 1 (page 14)" refers to Centocor's response to Abbott Fact 1 as set out in Paper 238, page 14.

Additional findings as necessary may appear in the Discussion portion of the opinion.

Technical background

The Board invited both parties to submit a tutorial on the subject matter involved in the interference. Paper 276, page 5.

Both parties accepted the invitation. Abbott Tutorial, Paper 405 and Centocor Tutorial, Paper 409. The Board appreciates both tutorials.

Both tutorials are generally consistent so we borrow liberally from both.

Interleukin **12**—known as IL-12—is a protein made in the body by humans. Paper 405, page 4; Centocor, page 1.

In biotechese, IL-12 is referred to as a "cytokine."

IL-12 is a useful protein unless—as Yogi Berra would say—it is not a useful protein.

IL-12 plays a role in immune response.

In other words, when foreign material invades the body, IL-12 might be released as part of a body's immune response.

In biotechese, the foreign material is known as an "antigen" (from "**anti**body **gen**erating substances")

Unfortunately, IL-12 can be overproduced in the body (or as Abbott states "deregulated"—Paper 405, page 4) and becomes what might be referred to as a "self-antigen."

Overproduction is not a good thing and is said to lead to such immune diseases as rheumatoid arthritis, psoriasis and Crohn's disease—to name a few. Paper 409, page 1.

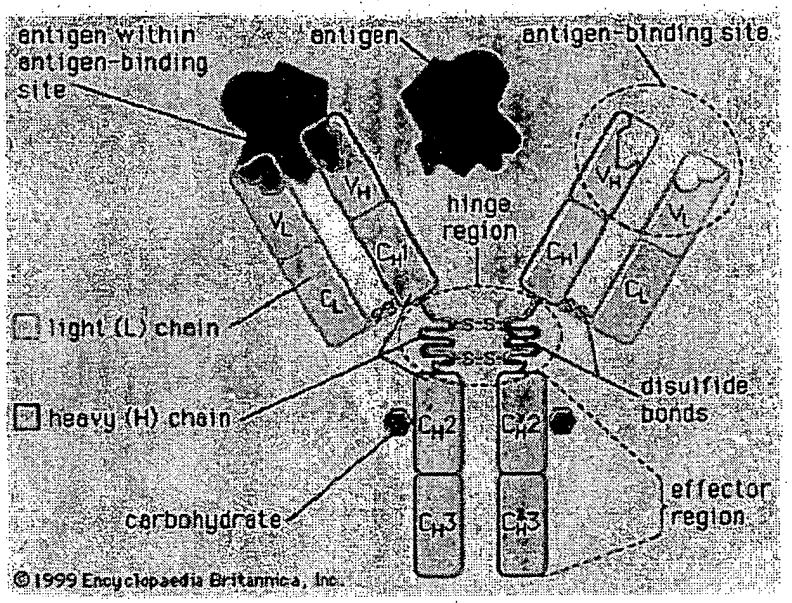
When overproduction occurs, one way to bring IL-12 back into a "useful" role is to "tie" some of it up so that less IL-12 is available.

Both parties have discovered that one way to do "tie" up excess IL-12 is to bind at least some of it with an antibody.

Key to the discovery, is that the antibody be a "human antibody" (as opposed to say a "mouse antibody").

Not only does the antibody have to "bind" to IL-12, but it must also "neutralize" IL-12.

The diagram below, provided by Centocor (Paper 409, page 2), shows one antigen bound to an antibody.

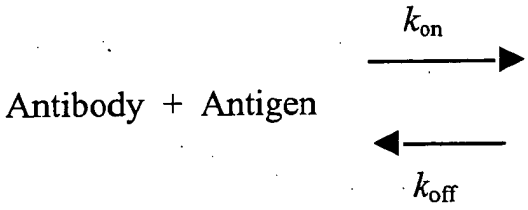


Schematically depicted is an antigen bound to an antibody

As can be seen from the diagram, there are two antigens (the irregular shaped black objects). The antibody is shown as a generally Y-shaped object. One of the antigens (i.e., IL-12) is shown bound to the antibody. The other is shown floating around and is not bound to the antibody.

Whether the antigen is sufficiently bound to the antibody depends on the strength of interaction between the antigen and antibody. Paper 409, page 4. The rate of binding of antigen and antibody at a particular concentration is a constant identified as k_{on}. Another constant (k_{off}) is the rate at which the antigen dissociates from the antibody. Paper 409, page 4. Centocor explains as follows (Paper 409, pages 4-5):

a typical antigen-antibody binding and dissociation can simply be represented as follows:



Equilibrium is reached when the rate at which new antigen-antibody complexes are formed equals the rate at which the antigen-antibody complexes dissociate. At equilibrium:

$[\text{Antigen}][\text{Antibody}] \cdot k_{on} = [\text{Antigen-Antibody}] \cdot k_{off}$

K_d is a value that describes the relative relationship of k_{off} and k_{on} when the reaction is at equilibrium.

$$k_{off} / k_{on} = K_d$$

In a footnote (Paper 409, page 5 n:1) , Centocor explains:

> [Antigen] is a notation for the concentration of Antigen; likewise, the notation [Antibody] refers to the concentration of the Antibody. [Antigen-Antibody] refers to the concentration of the antigen-antibody complex.

The parties tell us that there are various ways to measure antibody-antigen affinities. According to Centocor, one method is using Surface Plasmon Resonance (SPR). Paper 409, pages 5-7. According to Abbott, another method is via Receptor Binding Assay (RBA). Paper 405, pages 11-12. Yet another method according to Abbott is via PHA Blast Neutralization Assay (PHA). Paper 405, pages 12-13. At this point, we will note that Abbott conducted some neutralization tests, but Centocor disputes whether the results of the Abbott tests confirm neutralization. More about neutralization later in the opinion.

Centocor has the following to say about neutralization (Paper 409, page 7):

> Neutralization refers to the ability of an antibody to inhibit one or more biological activities of the antigen to which it binds. Accordingly, the ability of an antibody to "neutralize" an antigen may be evaluated by examining the extent to which presence of the antibody in an experimental system affects a biological activity of the antigen. According to such an experiment, a baseline would first be established by adding the antigen alone to an experimental system and measuring the effect of the antigen on a selected biological activity. Once the effect of the antigen on the biological activity was established, the antibody is then introduced to the system and the effect, if any, on the biological activity is monitored.
>
> In the case of IL-12, one known activity of IL-12 is the stimulation of interferon gamma production. Accordingly, the ability of an antibody to neutralize IL-12 may be assessed by evaluating the effect on the antibody on IL-12 stimulated interferon gamma production.

Collaboration between BASF, GI and CAT

BASF, GI and CAT collaborated in an attempt to make human antibodies which would bind to and neutralize IL-12. Centocor response to Abbott Fact 1 (page 14).

The collaboration involved a project known as "Isolation of Human Antibodies which Neutralize Human IL-12" ("**Project**"). Centocor response to Abbott Fact 2 (page 14).

In general, and as part of the Project, scientists at BASF selected IL-12 as a target and evaluated and developed animal models. Scientists at CAT and BASF conducted affinity maturation and antibody expression. Scientists at GI engaged in human IL-12 production and bioassay evaluation of candidate antibodies. Scientists at CAT worked on selection and affinity maturation of candidate antibodies that bind to human IL-12 using phage display technology. Centocor response to Abbott Fact 3 (pages 14-15). Phage display technology was described by Duncan during cross-examination. Ex 2066, page 14:18 to page 15:5.

Pursuant to the collaboration between BASF, GI, and CAT, a series of "milestones" were set, documenting goals to be achieved during the collaboration. Admitted Abbott Fact 4 (page 15). *See also* Ex 1358 (Milestone 1 Report), Appendix 7.1 setting out a schedule of research program for the anti-IL-12 project—discussed by Elvin during cross (Ex 2067, page 36:12-16)

Milestone Reports

Milestone Reports documenting purported achievements of milestones were generated. Ex 1358 (Milestone 1), Ex 1365 (Milestone 2), Ex 1402 (Milestone 3b), Ex 1403 (Milestone 4) and Ex 1404 (Milestone 5). Centocor response to Abbott Fact 5 (page 15).

Milestone 1 Report (1) is dated 13 September 1995 (Ex 1358, third page numbered page 1) and (2) was co-authored by Duncan and Elvin of CAT (Ex 1358, page 3/13, Ex 1324, ¶ 7 (Duncan direct) and Ex 1323, ¶ 6 (Elvin direct)).

Milestone 2 Report is (1) dated 12 December 1995 (Ex 1365, page 3/13) and (2) was co-authored by Duncan and Elvin (Ex 1365, page 3/13, Ex 1324, ¶ 11 (Duncan direct) and Ex 1323, ¶ 9 (Elvin direct)).

Milestone 3b Report is (1) dated 15 July 1996 (Ex 1402, fourth page), (2) identifies (a) Elvin, (b) Leila du Fou and (c) Duncan as its authors (*id.*) and (3) would have been received by Kamen (Ex 1321-revised, page 8:5).

Milestone 4 Report (1) is dated 28 November 1997 (Ex 1403, third page), (2) identifies (a) Elvin, (b) du Fou, (c) Stephen Smith, and (d) Elaine Derbyshire and (e) Duncan as its authors (id.) and (3) would have been received by Kamen (Ex 1321-revised, page 10:18-19).

Milestone 5 Report (1) is dated 26 August 1998 (Ex 1404, page 1), (2) identifies (a) Derbyshire, (b) Elvin, (c) Sara Carmen, (d) Stephen Smith, (e) Thor Holtet and (f) Duncan as its authors, and (3) would have been received by Duncan (Ex 1321-revised, page 12:7).

Teams at BASF, GI and CAT

"Teams" of employees at BASF, GI and CAT worked on the project.

BASF: Salfeld, Tracey, Banerjee collaborated at BASF toward accomplishing human antibodies which bind to human IL-12 and which neutralize human IL-12. Admitted Abbott Fact 11 (page 17).

GI: Veldman, Widom and Venturini collaborated at GI on the Project. Admitted Abbott Fact 12 (Page 17).

CAT: Duncan and Elvin collaborated at CAT to isolate human antibodies. Centocor response to Abbott Fact 13 (pages 17-18); see also Ex 2066, page 19:8-11 (Duncan cross). There is a factual dispute between Abbott and Centocor on the precise nature of the Duncan and Elvin collaboration. Abbott maintains, and Centocor denies, that Duncan and Elvin collaborated on the accomplishing of human antibodies to human IL-12 which *neutralize* human IL-12. Abbott Fact 13 and Centocor response to Abbott Fact 13. We resolve the factual dispute in favor of Abbott. The factual dispute involves use by Abbott witnesses of the term "inhibition"

while the count states, and Centocor uses, the term "neutralize." *See e.g.*, Abbott Reply, paper 238, page 12:9-19. The use of the two terms in this "biotech" interference confirms our experience—based on numerous biotech interferences which have come before the Board—that precise consistent language in biotech cases while perhaps a "hope" is nothing but a "hopeless illusion." At the end of the day and for reasons explained herein, in this case the Abbott "biotechese" term "inhibition" means essentially the same thing as the Centocor "biotechese" term "neutralization"—at least as that term is used in the Centocor portion of the count. We therefore find that Duncan and Elvin collaborated on the accomplishing of human antibodies to human IL-12 which *neutralize* human IL-12. An alternative, but equivalent finding would be: Duncan and Elvin collaborated on the accomplishing of human antibodies to human IL-12 which *inhibit* human IL-12.

General interactions between BASF, GI and CAT

During their work on the IL-12 antibody project, (1) Salfeld, Tracey, and Subhashis (BASF), (2) Veldman, Widom, and Venturini (GI) and (3) Elvin and Duncan (CAT) routinely collaborated. Centocor response to Abbott Fact 14 (page 18).

During at least 1995-1996, Veldman and her team at GI provided Duncan and his team at CAT with human IL-12. Admitted Abbott Fact 15 (page 18).

Elvin (CAT) obtained human antibodies to the human IL-12 received from GI, using as a starting material in his experiments so-called "libraries" or collections of human antibodies, which are derived from a human source. Admitted Abbott Fact 16 (pages 18-19).

Elvin found human antibodies that bound to the human IL-12. Admitted Abbott Fact 17.

Elvin and his team at CAT sent the human antibodies that bound to the human IL-12 to Salfeld and his team at BASF. Admitted Abbott Fact 18 (page 19).

Scientists at BASF expressed and isolated the human antibody fragments received from CAT and Salfeld sent them for subsequent testing at GI. Centocor response to Abbott Fact 19 (page 19).

Veldman and her team at GI used the expressed human antibody fragments from BASF to perform assays called "receptor binding assays" (RBA) and "PHA blast assays". Centocor response to Abbott Fact 21 (page 20).

The language of the Count

Count 1 is reproduced earlier.

With language of involved Centocor claim 1 and involved Abbott claim 1 incorporated therein, Count 1 reads (paragraphing, bracketed matter and italics added):

> [(1)—Centocor claim 1] [a]n isolated human antibody, or an antigen-binding portion thereof, that binds to human IL-12, wherein said human antibody is a *neutralizing* antibody
>
> or
>
> [(2)—Abbott claim 1] [a]n isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a K_d of 1×10^{-10} M or less and a k_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance.

Admitted Abbott Fact 22 (page 20).

"Neutralization" is defined in the specification of the involved Centocor application as follows (italics added):

As used herein, the term "neutralizing antibody" refers to an antibody that can *inhibit* an IL-12-dependent activity by about 20-120%, preferably by at least at 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% or more depending on the assay. The capacity of an anti-IL-12 antibody to *inhibit* an IL-12-dependent activity is preferably assessed by at least one suitable IL-12 protein or receptor assay, as described herein and/or as known in the art.

Ex 1031, page 23:8-13. Centocor response to Abbott Fact 23 (pages 20-21)

Abbott's conception "story"

Abbott has presented the following "story" in support of conception. For the most part, Centocor admits that the Abbott conception "story" is accurate.

Salfeld sent a Memo (Ex 1339, dated 30 July 1993,) inviting various persons to attend a discussion on targets which were the subject of a prior "brain storming" meeting. Admitted Abbott Fact 27 (page 22). The discussion was to take place on 8/4/93 (4 August 1993). Ex 1339, unnumbered page 1.

The Memo (Ex 1339) is a document consisting of 22 unnumbered pages. The preferred practice would have been to "Bates" number the pages. The only pages with information are unnumbered pages 1, 15 and 16. The remaining pages are redacted. The Memo is addressed to 22 individuals, including the following individuals who have testified on behalf of Abbott: (1) Tracey, (2) Banerjee, (3) Ghayur and (4) Kamen. *See* unnumbered page 1.

The "brain storming" meeting referred to in the 30 July 1993 Memo took place on or about 16 July 1993 at BASF in Cambridge, Massachusetts. Admitted Abbott Fact 28 (page 22).

Salfeld (Ex 1318 ¶¶ 13-14), Tracey (Ex 1319 ¶¶ 13-14) and Banerjee (Ex 1320 ¶ 14) attended the "brain storming" meeting.

Other participants in the meeting were Ghayur and Kamen. Admitted Abbott Fact 36 (page 24).

During the brain storming meeting Salfeld, Tracey and Banerjee discussed a number of potential new antibody targets, including IL-12. Admitted Abbott Fact 30 (page 22).

During the brain storming meeting, Banerjee gave a presentation using hand written transparency sheets and transparency sheets copied from paper documents onto an overhead projector to help discuss how IL-12 would be a good target for the development of a human antibody for BASF to pursue. Admitted Abbott Fact 31 (page 23).

At the brain storming meeting, Banerjee suggested targeting IL-12 because it was located upstream of interferon gamma (IFN-γ), a cytokine involved in various pathologies. Admitted Abbott Fact 32 (page 23); Ex 1320 ¶ 12 (page 6:6-8). *See also* Ex 1339, page 16:2-7.

During the brain storming meeting, Salfeld, Tracey and Banerjee discussed the state of the art of IL-12. The state of the art is said to be summarized on unnumbered page 15 of the Memo (Ex 1339). Admitted Abbott Fact 33 (page 23).

As of 30 July 1993, little data had been published regarding the role of IL-12 in various inflammatory disease models and there were no known publications disclosing IL-12 human antibodies that neutralized IL-12. Centocor response to Abbott Fact 34 (pages 23-24).

Following the brain storming meeting, Banerjee made a presentation to Kamen (President of BASF), and to the senior staff at BASF. Banerjee explained why he believed IL-12 would be a good antibody target for BASF to pursue in collaboration with CAT. Admitted Abbott Fact 38 (page 24).

The 30 July 1993 Memo memorialized the contents of the brain storming meeting session. Admitted Abbott Fact 39 (page 25).

The 30 July 1993 Memo was prepared in anticipation a future meeting on 4 August 1993. Admitted Abbott Fact 40 (page 25).

Kamen received and reviewed the 30 July 1993 Memo. Admitted Abbott Fact 41 (page 25).

Ghayur also received the 30 July 1993 Memo. Admitted Abbott Fact 42 (page 25).

During the brain storming session, at least Banerjee, Tracey and Salfeld together conceived of an isolated human antibody to human IL-12 that binds human IL-12 and neutralizes human IL-12. Admitted Abbott Fact 37 (page 24). See also Ex 1339, unnumbered page 16:

> Since IL-12 may be the primary inducer of the differentiation of CD4+T cells to the TH1 phenotype after stimulation by antigens, blocking the IL-12 may block the induction of inflammatory-type T cells, and may in fact switch the response to a TH2-type response which may reduce the pathogenic cellular immune responses. In addition, IL-12 is also involved in the maturation of cytotoxic T cells which have also been implicated in some ... diseases.

The subject matter of the Count (an isolated human antibody that binds to human IL-12 and neutralizes human IL-12) was jointly conceived by at least Salfeld, Banerjee, and Tracey no later than 30 July 1993.

Admitted Abbott Fact 26 (pages 21-22). *See also* Admitted Abbott Fact 46 (page 26).

After the brain storming meeting (16 July 1993), and with more information considered at the meeting on 4 August 1993, at least Tracey, Banerjee and Salfeld chose IL-12 as a target for a human antibody. Admitted Abbott Fact 35 (page 24) and Admitted Abbott Fact 45 (page 26).

Corroboration of conception

While Centocor does not seem to contest conception, we make the following observations with respect to non-inventor witnesses who testified for Abbott.

Ghayur and Kamen are said to have confirmed that during the 16 July 1993 brain storming meeting, at least Banerjee, Tracey and Salfeld together conceived of an isolated human antibody to human IL-12 that binds human IL-12 and neutralizes human IL-12. Admitted Abbott Fact 47 (pages 26-27).

Ghayur and Kamen also are said to have confirmed that an isolated neutralizing human antibody to human IL-12 that binds to IL-12 was conceived of or thought of by at least Banerjee, Salfeld and Tracey no later than 30 July 1993. Admitted Abbott Fact 48 (pages 26-27).

During the time period of 1993 to 1999, Kamen was familiar with the work of Tracey, Salfeld and Banerjee related to the identification of new targets for BASF's human monoclonal antibody program. Admitted Abbott Fact 49 (page 27).

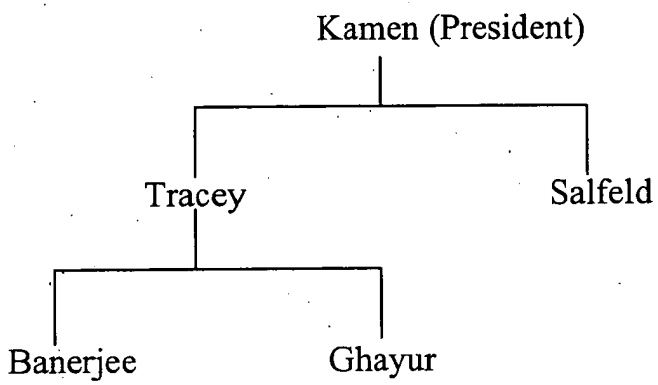
BASF was a relatively small company in 1993. Admitted Abbott Fact 55 (page 28). See also Ex 2068, page 30:1-5.

During 1993 to 1999, Tracey and Salfeld reported directly to Kamen. Admitted Abbott Fact 50 (page 27).

Banerjee reported directly to Tracey during 1993 to 1999. Admitted Abbott Fact 51 (page 27).

Ghayur—a BASF Senior Scientist—appears to have reported to Tracey. Ex 1322, ¶ 4 (page 2:1-3).

Graphically, a relevant portion of the BASF organization chart would appear to be the following.



Kamen discussed the BASF human monoclonal antibody program, including the human IL-12 antibody project, with each of Tracey, Salfeld and Banerjee on numerous occasions. Admitted Abbott Fact 52 (page 27).

Kamen frequently held numerous informal discussions with Tracey and Salfeld regarding the identification of new targets for BASF's human monoclonal antibody program. Admitted Abbott Fact 53 (page 27).

Kamen spoke with Tracey and Salfeld just about every day. Admitted Abbott Fact 55 (page 28).

Kamen held weekly one-on-one meetings with Tracey and Salfeld regarding their work projects. Tracey or Salfeld would discuss with Kamen their work with respect to the identification of new targets for BASF's human monoclonal antibody program. Admitted Abbott Fact 56 (page 28).

In 1993, Kamen held occasional conversations with Banerjee, including conversations regarding the identification of new targets for BASF's human monoclonal antibody program. Admitted Abbott Fact 54 (page 28).

In 1993, Ghayur had frequent discussions with Banerjee, including discussions regarding biasing the immune system away from TH1 cells to provide therapies for TH1 related pathologies. Admitted Abbott Fact 57 (page 28).

Ghayur recalls that in 1993, Banerjee led collaborative discussions about pursuing human IL-12 as a potential new target for developing therapeutic human antibodies to human IL-12. Admitted Abbott Fact 58 (page 28).

Ghayur remembers that in 1993, Banerjee was adamant about the important role of TH1 cells in inflammatory diseases and the role of IL-12 in influencing IFN-γ. Admitted Abbott Fact 59 (pages 28-29).

Abbott's actual reduction to practice "story"

In order to actually reduce to practice the "conception," at least the following "steps" needed to occur. *First*, a human antibody needed to be isolated. Isolated human antibodies were given the name "Joe" followed by a number. As will become apparent, one the first relevant antibodies tested was assigned the name Joe 7. *Second*, tests needed to be performed to determine if the "antibody" would bind to human IL-12. *Third*, additional tests had to be performed to further determine if binding of the "antibody" to human IL-12 "neutralized" the human IL-12.

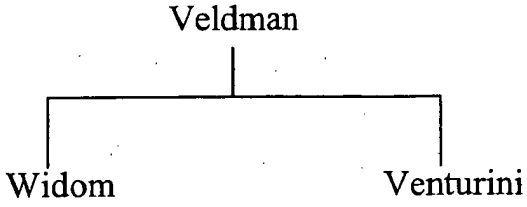
These steps occurred not at one company; rather various parts of each step occurred at BASF, GI and/or CAT.

Our findings are set out in essentially the order presented by Abbott.

Activities at GI

Veldman, Venturini and Widom worked in close proximity to one another and shared laboratory resources including laboratory benches, instruments and reagents. Admitted Abbott Fact 60 (page 29).

The organization structure, shown in graphic terms, is the following.



It was common for Veldman, Venturini and Widom to discuss their experimental results as soon as they were obtained. Admitted Abbott Fact 60 (page 29).

It was the standard practice of Veldman, Venturini and Widom to immediately copy the results of their laboratory experiments, including the raw data, calculations, summarized data and illustrations of the data, and to provide one another with copies. Admitted Abbott Fact 61 (page 29).

Veldman "work"

Veldman oversaw, worked, and collaborated with, Widom and Venturini relating to conducting PHA and RBA assays with respect to antibodies that CAT scientists had isolated using IL-12. Centocor response to Abbott Fact 62 (pages 29-30).

Veldman was the direct supervisor of Widom and Venturini. Ex 2070, page 23:20 to page 24:1.

Veldman regarded both Widom and Venturini to be competent scientists and trusted their scientific work. Ex 2070, page 67:15 to page 68:1.

Veldman, Widom and Venturini did not isolate human antibodies to IL-12 from scFv libraries. Centocor response to Abbott Fact 62. Isolation occurred at CAT. Isolated antibodies were given by CAT to BASF. As noted earlier, the isolated antibodies (or fragments of isolated antibodies) were assigned a "Joe" number.

Veldman gave the "Joe" human antibody fragments received from BASF to Widom and Venturini to use in a PHA Assay or RBA. Admitted Abbott Fact 63 (page 30).

Widom and Venturini performed PHA Assays and RBA. Admitted Abbott Fact 63. While Veldman statements about what Widom and Venturini did is hearsay, Centocor nevertheless admitted Abbott Fact 63. Centocor had good reason to admit the fact (as well as other Veldman hearsay testimony) given direct testimony by Widom and Venturini—which we discuss *infra*.

Widom performed RBAs to determine whether the antibodies received from BASF *inhibited* binding of IL-12 to IL-12 receptors. Centocor response to Abbott Fact 64 (page 30). As noted earlier, Centocor is unwilling to agree that "inhibiting" and "neutralization" are the same thing in the context of this case. We disagree with Centocor. An alternative finding would be Widom performed RBAs to determine whether the antibodies received from BASF *neutralized* human IL-12.

On 8 May 1995, Veldman sent Duncan 1 mg of human IL-12 to screen the antibody fragment scFv antibody phage libraries at CAT. Admitted Abbott Fact 65 (page 30).

On or about 23 May 1995, Veldman performed a large scale biotinylation of human IL-12 to provide biotinylated human IL-12 to CAT. Admitted Abbott Fact 67 (page 31).

On 23 May 1995, Veldman sent 900 µL of biotinylated IL-12 at a concentration of 2.5 mg/ml to Duncan. Admitted Abbott Fact 68 (page 31).

The biotinylated human IL-12 that Veldman sent on 23 May 1995 to Duncan was used by Elvin (also of CAT) to screen antibody fragment scFv phage display libraries "1" and "2" for IL-12 binding antibodies or antibody fragments. Admitted Abbott Fact 69 (page 31). Veldman was not present when Elvin did his work. Ex 2070, page 53:16-18. Testimony by Veldman about what Elvin might have done is hearsay (to the extent it is offered to prove what Elvin did). However, Elvin testimony discussed *infra* obviates any hearsay concern and provided Centocor with a basis upon which to admit Abbott Fact 69. The Veldman testimony serves to indicate what she believes what Elvin did as opposed to direct evidence of what occurred in Elvin's laboratory. We rely on the Elvin testimony for what occurred in his laboratory.

Veldman (GI), Duncan (CAT) and Elvin (CAT) had numerous discussions regarding the results of the screening of the antibody fragment scFv phage display libraries using the human IL-12 obtained by them. Admitted Abbott Fact 70 (page 31).

Veldman received purified human scFv antibodies Joe 7 and Joe 10 from White (BASF) along with a White letter dated 31 August1995 (Ex 1391). Admitted Abbott Fact 71 (page 31).

The Joe 7 and Joe 10 scFv antibodies bound to human IL-12. Admitted Abbott Fact 72 (page 31). EX 1327 ¶ 39.

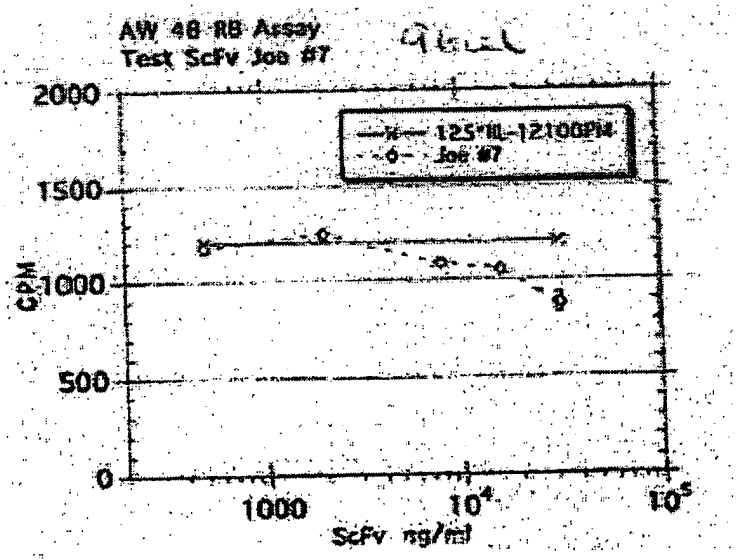
The Joe 7 and Joe 10 scFv antibodies that bound to human IL-12 inhibited binding of human IL-12 to its receptor by a least 20% and not less than 10%. Centocor response to Abbott Fact 72 (pages 31-32).

Veldman gave the human antibody scFvs designated "Joe" [including Joe 7 and Joe 10] received from White to Widom to perform RBAs. Centocor response to Abbott Fact 73 (page 32).

Beginning on or about 18 September 1995, Widom determined the inhibition by antibody variable region fragment (scFv) Joe 7 and antibody variable region fragments (scFv) Joe 10 in a RBA. Ex 1327 ¶ 40 [describing what Widom is said to have done]; Ex 1344 [recording on pages 82-90 Widom experiments].

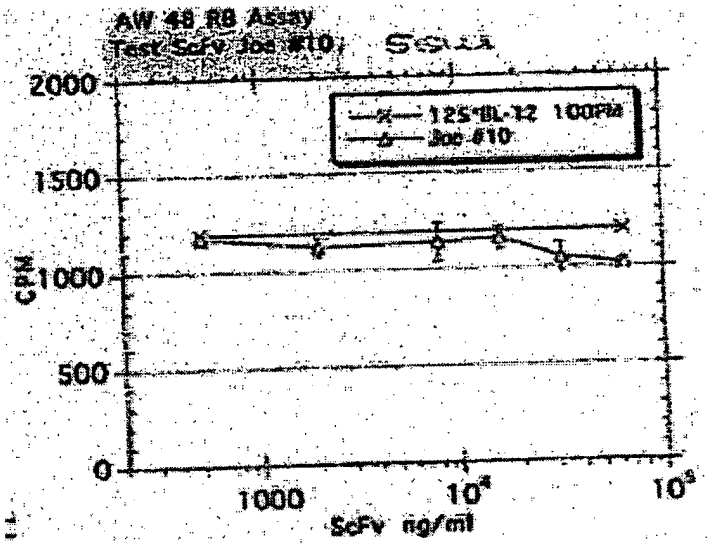
Veldman believes, and Widom testimony confirms, that Widom graphically depicted inhibition by antibody scFv Joe 7 and Joe 10 to PHA blast stimulated IL-12 receptors. Ex 1327 ¶ 41 [Veldman direct]; Ex 1329, ¶ 9 [Widom direct]; Ex 1344 [Widom laboratory notebook].

The following two graphs appear on page 89 [dated 19 September 1995—subsequently "witnessed" by Gimlich of GI] of Widom laboratory notebook 4621 [Ex 1344].



Graph 1

Graph 1 depicts the results of a Widom RB Assay of Joe 7



Graph 2

Graph 2 depicts the results of a Widom RB Assay for Joe 10

Graph 1 shows increasing inhibition with higher concentrations of antibodies Joe 7 and Joe 10, respectively, as the hatched line with circles and triangles (CPM of PHA stimulated blast cells), respectively, slopes downward [note lines with circles] versus the line having the designation "X" [meaning the solid line at about 1200 CPM]. Centocor response to Abbott Fact 77 (page 33).

According to Veldman, the graphs show increasing neutralization with higher concentrations [axis with ScFv ng/ml]. Ex 1327—revised, ¶ 41. Widom agrees. Ex 1329, ¶¶ 9 and 21.

The inhibition of the Joe 7 antibody was identified as being 26.64%. Centocor response to Abbott Fact 78 (page 33).

The inhibition of the Joe 10 was identified as being 14.8%. Centocor response to Abbott Fact 78 (page 33).

On or around 19 September 1995, Veldman understood and appreciated that the Joe 7 and the Joe 10 antibodies bound to human IL-12

and neutralized human IL-12 binding by at least 20% and not less than 10%. Ex 1327, ¶ 42.

The Veldman understanding is consistent with data recorded in the Widom laboratory notebook. Id.

The Widom data includes the two graphs reproduced above.

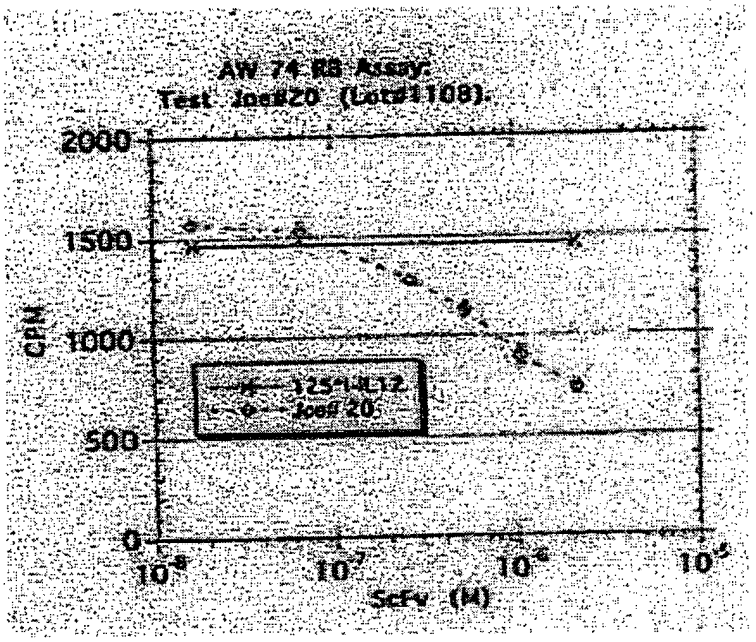
By fax dated 20 September 1995, Veldman transmitted the inhibition data, *inter alia*, to Salfeld (BASF), White (BASF) and Banerjee (BASF). Ex 1327—revised, ¶ 43 [Veldman direct]; Ex 1373 [copy of fax—"As you can see the inhibition by Joe 7 (26% in assay 2) is quite good."]. See also Centocor response to Abbott Fact 80—"Veldman reported inhibition results for Joe 7 and Joe 10 to some of her collaborators at some point in time."

Beginning on 22 September 1995, Widom determined the inhibition of IL-12 binding to its receptor by antibody variable region fragment (scFv) Joe 20 and antibody variable region fragments (scFv) Joe 22 in a RBA. Centocor response to Abbott Fact 81 (pages 34-35).

Widom graphically depicted inhibition by antibody scFv Joe 20 and Joe 22 to PHA blast stimulated IL-12 receptors using the non-specific binding subtracted counts summarized at page 32 of Widom laboratory notebook 4746 (Ex 1346). Centocor response to Abbott Fact 81 (pages 34-35). We add that while Widom started experiments involving Joe 20 and Joe 22 on 22 September 1995, the graphical depictions appear on a laboratory notebook page dated 14 November *1994*. We believe Widom mistakenly entered a 1994 date in her laboratory notebook when she should have entered 1995. Why? *First*, facially Notebook 4746 was assigned to Widom on 7 November 1995. Ex 1346, second page. *Second*, pages 26-29 are dated in November of 1995. *Third*, neither Veldman nor Widom claim to have experimented with Joe 20 or Joe 22 in 1994. *Fourth*, in her direct

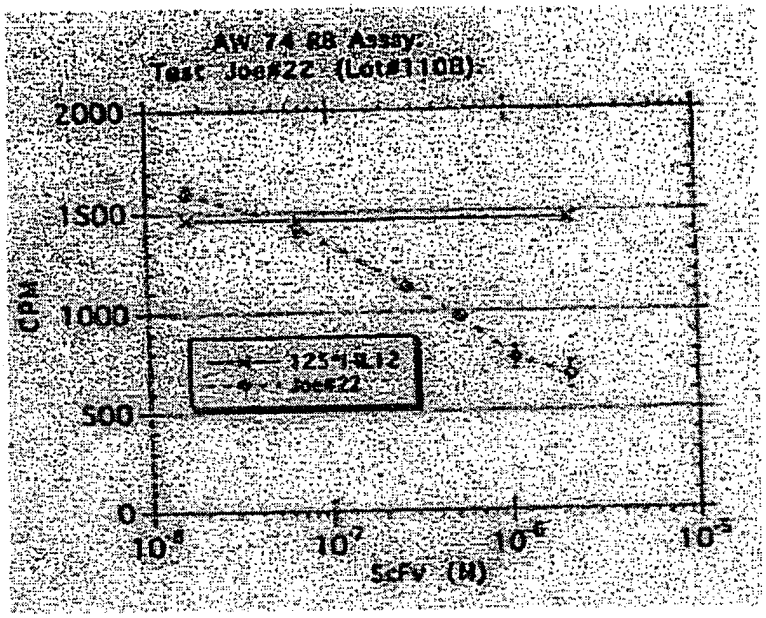
testimony, Widom indicates the date is 15 November 1995. Ex 1329, page 4: *see* Table.

The following two graphs appear on page 32 [mistakenly dated 16 November 1994—subsequently "witnessed" by Wood of GI] of Widom laboratory notebook 4746 [Ex 1346].



Graph 3

Graph 3 depicts the results of a Widom RB Assay of Joe 20



Graph 4

Graph 4 depicts the results of a Widom RB Assay of Joe 22

Graph 3 shows increasing neutralization with higher concentrations of antibodies Joe 20 and Joe 22, respectively, as the hatched line with circles and squares (CPM of PHA stimulated blast cells), respectively, slopes downward versus the line having the designation "X". Centocor response to Abbott Fact 83 (page 35).

The neutralization of the Joe 20 scFv antibody was identified as being 49.75%. Centocor response to Abbott Fact 84 (page 36).

The neutralization of the Joe 22 scFv antibody was identified as being 53.57%. Centocor response to Abbott Fact 84 (page 36). *See also* **Graph 4**.

Veldman understood no later than about 16 November 1995 that the isolated Joe 20 and Joe 22 human scFv antibodies bound to human IL-12. Ex 1327—revised, ¶ 47 [Veldman direct].

Veldman understood, no later than about 16 November 1995 that the isolated Joe 20 and Joe 22 human scFv antibodies inhibited and neutralized

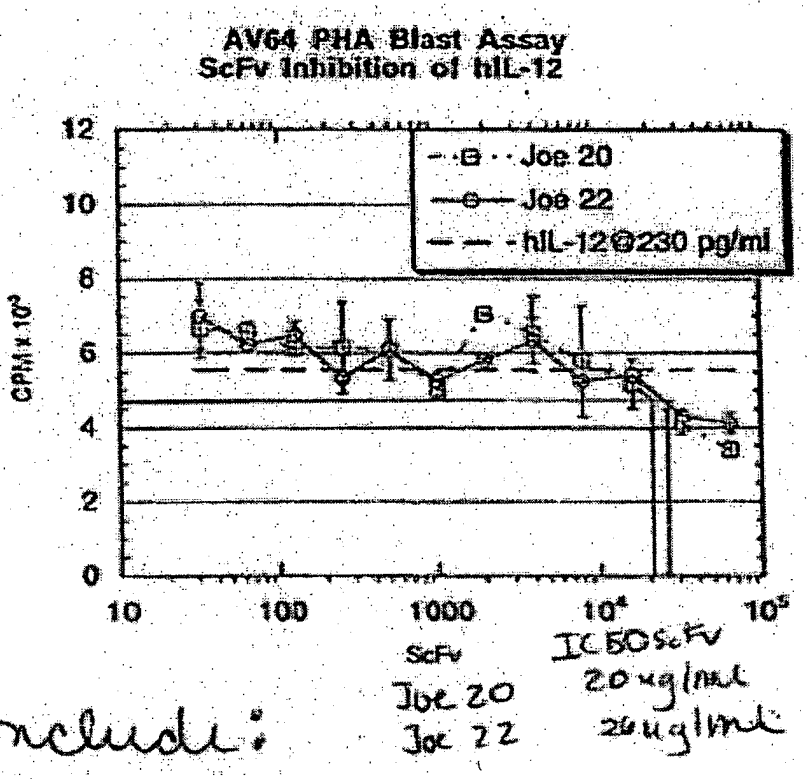
human IL-12 binding by a least 20% and not less than 10%. Ex 1327—revised, ¶ 47 [Veldman direct].

On 17 November 1995, Veldman reported via fax to Duncan at CAT the results of the Widom receptor binding assays for the "Joe" antibodies, including Joe 20 and Joe 22. Ex 1327—revised, ¶ 48 [Veldman direct]; Ex 1369 [fax dated 17 November 1995—"I am sending you the data of the receptor binding assay that ... [Widom] did with ... Joe #20 and Joe #22. Looks pretty good, huh!"

The Veldman 16 November 1995 understanding that Joe 20 and Joe 22 scFv antibodies inhibited human IL-12 activity and neutralized human IL-12 binding by a least 20% and not less than 10% was confirmed in Veldman's view by subsequent PHA Assays performed by Venturini in experiments recorded in pages 1-4 of Venturini laboratory notebook 4776. Ex 1327—revised, ¶ 49 [Veldman direct].

Beginning on 17 November 1995, Venturini conducted experiments using PHA Assays to determine neutralization of human IL-12 by scFv Joe 20 and Joe 22 antibodies. Joe 20 and Joe 22 bound to human IL-12. Centocor response to Abbott Fact 88 (page 37). See also Ex 1328, ¶¶ 23-24 [Venturini direct].

A graph of the Venturini experiments appears in Venturini laboratory notebook 4776. Ex 1350, page 4—page following numbered page 3 it being noted that page 4 does not appear to be numbered.



Graph 5

Graph 5 depicts results of Venturini experiments with Joe 20 and Joe 22

Graph 5 shows neutralization with higher concentrations of antibodies Joe 20 and Joe 22, as the hatched line with squares and circles (CPM of PHA stimulated blast cells), respectively, slopes downward versus the line having the designation "X." Ex 1327, ¶ 51 [Veldman direct]; Ex 1328, ¶¶ 21-28 [Venturini direct]; Ex 1350, page 4 [Venturini laboratory notebook]. Centocor maintains that at best the graphs show *inhibition* with

higher concentrations of antibodies Joe 20 and Joe 22. Centocor response to Abbott Fact 89 (page 37). Venturini's contemporaneous observation that "Joe 20 and Joe 22 are both *neutralizing*" is convincing evidence that Abbott proposed "neutralization" language is supported by the evidence. In any event, as noted earlier, "neutralization" and "inhibition" mean the same thing in the context of this case.

The last data point directed to Joe 20 in the graph represents a percent inhibition of cells of at least 20% and not less than 10%. Admitted Abbott Fact 90 (page 38).

The last data point directed to Joe 22 in the graph represents a percent inhibition of cells of at least 20% and not less than 10%. Admitted Abbott Fact 90 (page 38).

The results of the Venturini PHA Blast Assay for the Joe 20 and Joe 22 antibodies were reported to Duncan at CAT. Admitted Abbott Fact 91 (page 38).

The percent inhibition for Joe 7, Joe 20, and Joe 22 was reported in Section 7 of the Milestone 2 Report [Ex 1365—dated 18 December 1995] as 40%, 50%, and 50%, respectively. Admitted Abbott Fact 92 (page 38). Section 7 of the Milestone 2 Report is entitled "Neutralization Results". Ex 1365, page 9/13.

Venturini's PHA Blast Assay for Joe 20 and Joe 22 [**Graph 5**] appears on page 10/13 of the Milestone 2 Report.

In March of 1996 (Ex 1342, page 9) Veldman conducted PHA Assays for several of the "Joes" received from BASF. Admitted Abbott Fact 93 (page 38).

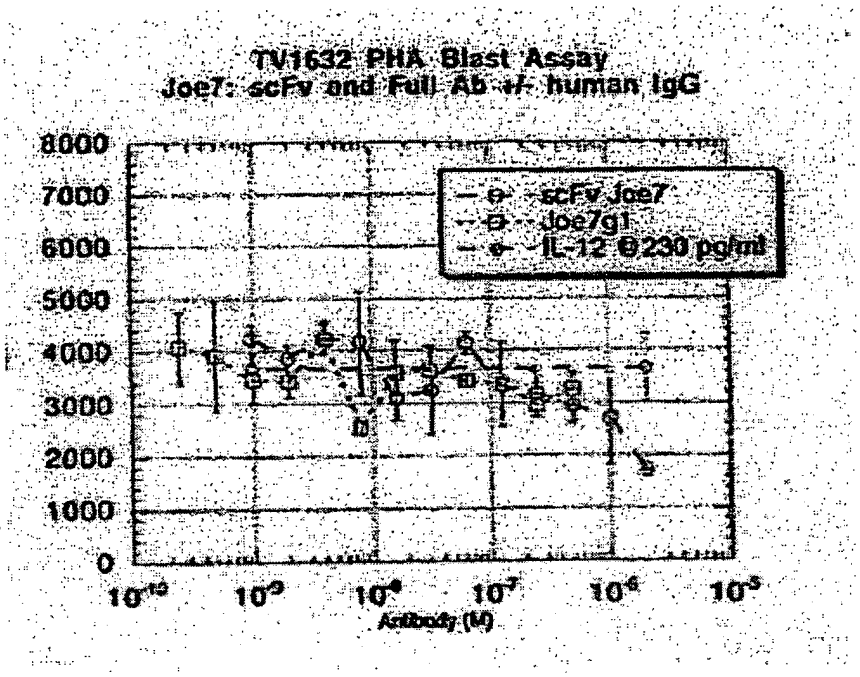
Veldman disclosed the experiments contained on pages 9-16 and 77-80 of Veldman laboratory notebook 4905 to Chen, who reviewed, signed,

and dated [on 19 November 1996] each of pages 9-16 and 77-80 of Veldman laboratory notebook 4905. Admitted Abbott Fact 94 (page 38). *See also* Ex 1342. Chen could not be located by Abbott and has not testified. However, Centocor admits Abbott Fact 94 and on that ground we feel comfortable making the finding.

Beginning on or about 16 February 1996, Veldman reproduced PHA Assays to further evaluate the ability of the antibody fragments (scFv) to human IL-12 to bind and inhibit IL-12 and the proliferation of PHA stimulated human blast cells. Veldman further evaluated the antibody variable region fragments (scFv) Joe 7 and Joe 10g1. Centocor response to Abbott Fact 95 (pages 38-39). *See also* Ex 1327 ¶ 56. Joe 10g1 was a full length Joe where as Joe 10 appears to have been a variable region fragment (scFv) Joe. Accordingly, Joe 10 and Joe 10g1 are different materials.

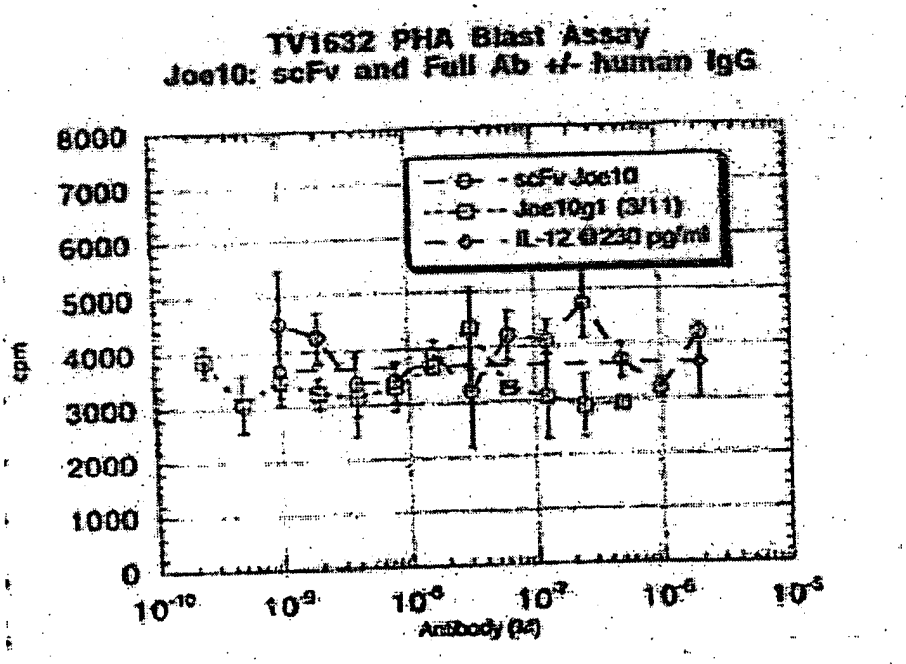
Veldman evaluated the ability of human antibody variable region fragments (scFv) Joe 7 and Joe 10g1 to block and inhibit the proliferation of PHA stimulated human blast cells in a PHA Blast Assay. Centocor response to Abbott Fact 96 (page 39).

Veldman graphed the neutralization of human IL-12 by Joe 7 and Joe 10g1 human antibodies and affixed the graphs she generated to pages 14-15 of Veldman laboratory notebook 4905 (Ex 1342). The graphs are reproduced below.



Graph 6

Graph 6 depicts results of Veldman experimental work with Joe 7



Graph 7

Graph 7 depicts results of Veldman experiments with Joe10g1

Graph 6 shows that less proliferation of the blast cells is obtained in the presence of scFv Joe 7 antibody, as seen by the hatched line with circles, which curves downward left to right, illustrating reduced proliferation of the blast cells in the presence of scFv Joe 7. Admitted Abbott Fact 98 (page 40).

Graph 7 shows that less proliferation of the blast cells is obtained in the presence of scFv Joe 10g1 antibody, as seen by the hatched line with circles, which curves downward left to right, illustrating less proliferation of the blast cells in the presence of scFv Joe 10. Admitted Abbott Fact 99 (page 40).

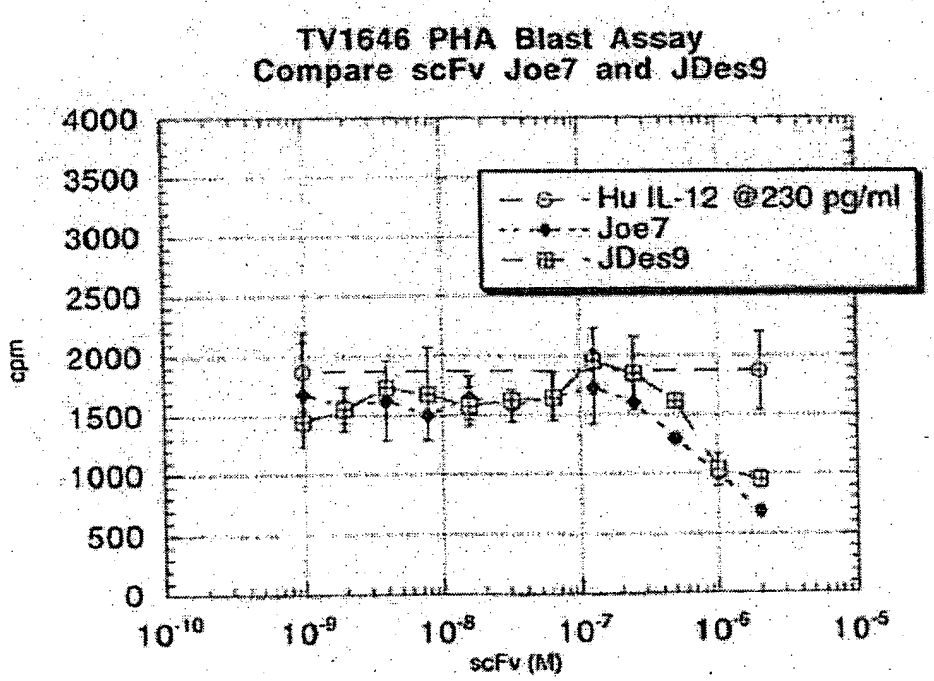
We observe that page 13 of Veldman laboratory notebook 4905 is dated 3-6-96, page 14 is dated 3-21-96 and page 15 is dated 3-6-96. What Veldman thinks happened is that she forgot on 6 March 1996 to sign page 14, discovered the non-signature on 21 March 1996 and the signed the notebook. Ex 2070, page 69:11 to page 70:7. Veldman's account is entirely plausible. Moreover, it does not matter in this case whether the work was done or 6 March 1996 or 21 March 1996. We also observe that in the middle of page 9 of Veldman laboratory notebook 4905 material is crossed out. We agree with Veldman that the strikethrough is no cause to otherwise doubt the entries or data in her laboratory notebook. Ex 2070, page 65:13 to page 68:13.

Veldman confirmed Venturini's prior experiment showing that the Joe 7 scFv antibody and Joe 10g1 antibody inhibited PHA blast proliferation at least by 20% and not less than 10%. Centocor response to Abbott Facts 100-102 (pages 40-41).

On or about 15 March 1996, Veldman conducted additional experiments in order to compare certain Joe antibodies, including further evaluation of the antibody variable region fragments (scFv) Joe 7 and Joe 9.

Venturini's experiments showed that these "Joes" bound to human IL-12 and inhibited PHA stimulated human blast cell proliferation by at least 20% and not less than 10% at certain concentrations on January 19, 1996. Admitted Abbott Fact 103 (page 41).

A graph representing Veldman's work appears on page 79 of her laboratory notebook 4905 (Ex 1343, page 79). Ex 1327—revised, ¶ 62 (pages 26-27).



Graph 8

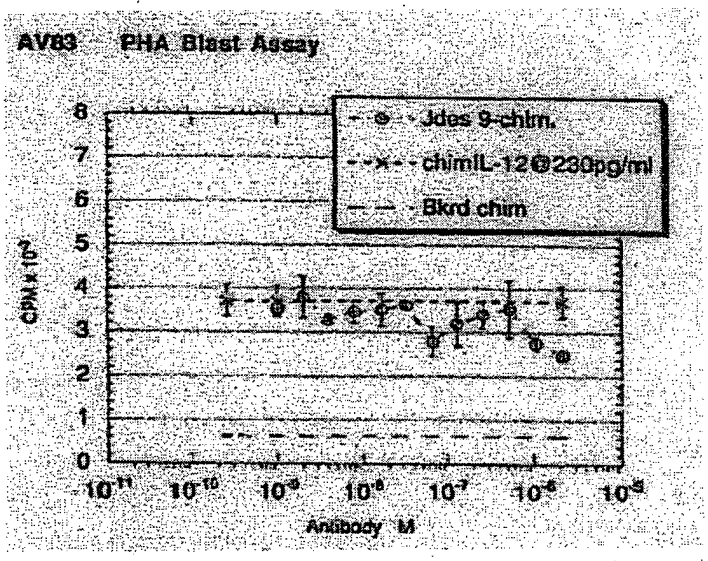
Graph 8 depicts Veldman experimental work with Joe 7 and Joe Des 9

The neutralization results of the PHA Assay that Veldman obtained on about 22 March 1996 (Ex 1343, page 79), confirmed the PHA Assay results that Venturini obtained in January of 1996 for the JDes9 (Ex 1353, page 95; Ex 1328, ¶ 44-47 [Venturini Direct]) and Joe 7 (Ex 1353, page 96; Ex 1328, ¶ 48-50 [Venturini direct]) human antibodies. The Veldman

results further confirmed Veldman's understanding and appreciation that JDes9 and Joe 7 neutralized human IL-12 and inhibited and neutralized PHA human blast cell proliferation by at least 20% and not less than 10%. Ex 1327, ¶¶ 62-63.

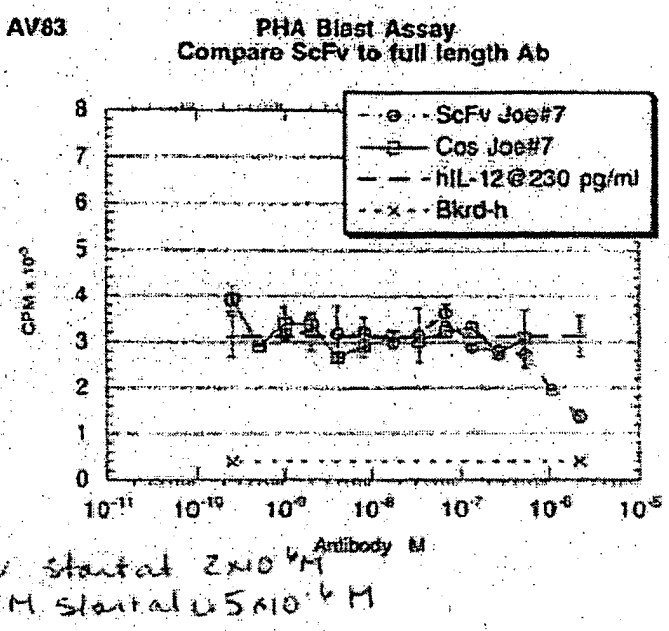
The record contains references to Joe 9 and JDes9. JDes9 was originally designated Joe 9, but somewhere along the line Joe 9 became Jdes9. Admitted Abbott Fact 228 (page 64).

Graphs representing Venturini's work appear on page 95 (JDes9) and on page 96 (Joe 7).



Graph 9

Graph 9 depicts Venturini experiments with Jdes 9 [Joe Des9]



Graph 10

Graph 10 depicts Venturini experimental work with Joe 7

The similarity between the Veldman Joe 7 [black dots] and Joe Des 9 [squares] curves and the Venturini Joe 7 [circles bottom graph] and Joe Des 9 curves [circles to graph] is apparent upon inspection.

Both the neutralization results of the RBA that Widom conducted and the Veldman PHA Assay using the same Joe 7 and "JDes9" scFv human antibodies showed neutralization by at least 20% and not less than 10%. Ex 1327—revised, ¶¶ 64-65 [Veldman direct]; Ex 1343 [Veldman laboratory notebook].

Widom "work"

Widom conducted experiments in 1995 and 1996 involving five human antibodies to human IL-12. The object of the experiments was to find out if the five human antibodies when bound would neutralize IL-12. Ex 1329, ¶ 9.

Widom used a "Receptor binding assay" (sometimes called a "RBA") to determine the ability of human antibodies to human IL-12 to neutralize radiolabelled human IL-12 binding to IL-12 receptors present on the surface of PHA stimulated human blast cells. Ex 1329, ¶¶ 9-10.

Widom determined that human antibodies having the designations Joe 7, Joe 9, Joe 10, Joe 20, and Joe 22 neutralized human IL-12 in amounts up to 50% inhibition. Ex 1329, ¶ 9.

The dates on which Widom conducted RBAs and the exhibit [laboratory notebook] in which experimental work is recorded is the following.

Exhibit # [Widom laboratory notebook number]	**Date**	**Joe number**
Ex 1344—[4621]	18 September 1995	Joe 7 & Joe 10
Ex 1345—[4621]	22 September 1995	Joe 7 & Joe 10
Ex 1346—[4746]	15 November 1995	Joe 20 & Joe 22
Ex 1347—[4880]	06 March 1996	JDes 9 & Joe 20
Ex 1348—[4880]	20 March 1996	Joe 7 & JDes 9
Ex 1349—[5009]	16 May 1996	JDes 9

Murtha-Riel, who witnessed pages 49-54 of Widom laboratory notebook 4880, passed away on 13 December 2003. Ex 1329 ¶ 14 [Widom direct]; Ex 1347 [Widom notebook—note that page 49 appears as "4"]; Ex 1401 [Murtha-Riel death certificate]. Admitted Abbott Fact 112 (page 43).

Widom used receptor binding assays to determine the neutralization of human IL-12 by human antibodies. Ex 1329, ¶ 18.

Widom followed the protocol described in Ex 1357 (pages 5 and 11-12) in performing the RBA in her experiments. Admitted Abbott Fact 114 (pages 43-44); Ex 1329, ¶ 19.

Widom determined that human antibodies designated as Joe 7 and Joe 10 bound to human IL-12 and neutralized human IL-12. Ex 1329, ¶ 21.

One object according to Widom's laboratory notebook was to see if certain results "are reproducible." Ex 1344, page 82. As Veldman noted during cross-examination, "[y]ou can never be certain of reproducibility until you show it." Ex 2070, page 80:8-9.

Widom determined the neutralization by antibody variable region fragment (scFv) Joe 7 and antibody variable region fragments (scFv) Joe 10 in a RBA in beginning on 18 September 1995. Widom recorded the details of the experiments she conducted on pages 82-90 of Widom laboratory notebook 4621. Ex 1329 ¶ 21.

Graphs are displayed on pages 89-90 of Widom laboratory notebook 4621. To make the graphs, Widom plotted the counts (CPM) on the Y axis and the antibody scFv concentrations in ng/ml on the X axis. Admitted Abbott Fact 117 (page 44); Ex 1329 ¶ 27; Ex 1344.

Graph 1, *supra*, shows the CPM of PHA stimulated blast cells wherein ^{125}I-IL-12 was bound as a line designated as "~~X~~" corresponding to the counts described at page 88 of Widom laboratory notebook 4621. Admitted Abbott Fact 118 (page 44); Ex 1344 [notebook]; Ex 1329, ¶ 28 [Widom direct].

The downward slope of the hatched line with squares (CPM of PHA stimulated blast cells) in the graph titled "AW48 RB Assay Test ScFv Joe

#7" [**Graph 1**, *supra*] versus the line having the designation "X" represents increasing neutralization with higher concentrations of antibody. Ex 1329, ¶ 28 [Widom direct].

The graph on page 89 of Widom laboratory notebook 4621 [**Graph 2**, *supra*] shows the CPM of PHA stimulated blast cells where ^{125}I-IL-12 was bound as a line designated as "X" corresponding to the counts described at page 88 of Widom laboratory notebook 4621 [Ex 1344]. Admitted Abbott Fact 121 (page 45).

The downward slope of the hatched line with triangles (CPM of PHA stimulated blast cells) versus the line having the designation "X" in the graph titled "AW48 RB Assay Test ScFv Joe #10"[**Graph 2**, *supra*] represents increasing neutralization with higher concentrations of antibody. Ex 1329, ¶ 29; Ex 1344.

On or about 19 September 1995, Widom obtained the results from the RBA started 18 September 1995. Admitted Abbott Fact 124 (page 46).

Page 88 of Widom laboratory notebook 4621 states that the Joe 7 scFv antibody neutralized the binding of radiolabelled human IL-12 by 26.64%. Ex 1344; Ex 1329, ¶ 30.

Page 88 of Widom Notebook 4621 states that the Joe 10 scFv antibody neutralized the binding of radiolabelled human IL-12 by 14.8%. Ex 1344; Ex 1329, ¶ 30.

On or about 19 September 1995, Widom understood that the Joe 7 scFv antibody and the Joe 10 scFv antibody bound to human IL-12 and neutralized human IL-12 by at least 20% and not less than 10%. Ex 1329, ¶ 31.

On or about 22 September 1995, Widom discussed with Veldman the results of the 19 September 1995 RBA Assay. Admitted Abbott Fact 128. Ex 1329 ¶ 32.

On about September 22, 1995, Widom repeated the 18 September 1995 experiments using the Joe 7 and Joe 10 scFv antibodies. Ex 1329, ¶ 33.

Widom obtained the antibody scFvs of Joe 7 and Joe 10 (lot 0921) from Veldman, who previously had obtained them from White of BASF. Admitted Abbott Fact 130 (page 47).

On 26 September 1995, Widom obtained the results from the RBA for the Joe 7 and Joe 10 scFv antibodies that she started 22 September 1995. Admitted Abbott Fact 132 (page 47). Ex 1329, ¶ 35.

Angela Widom wrote on page 108 of her laboratory notebook 4621:

Joe#7
Definitely
prove
to be
a scFv neutralizing
IL-12 and it
is dose dependent
% inh at 64 [ng/ml]
45%-58%.

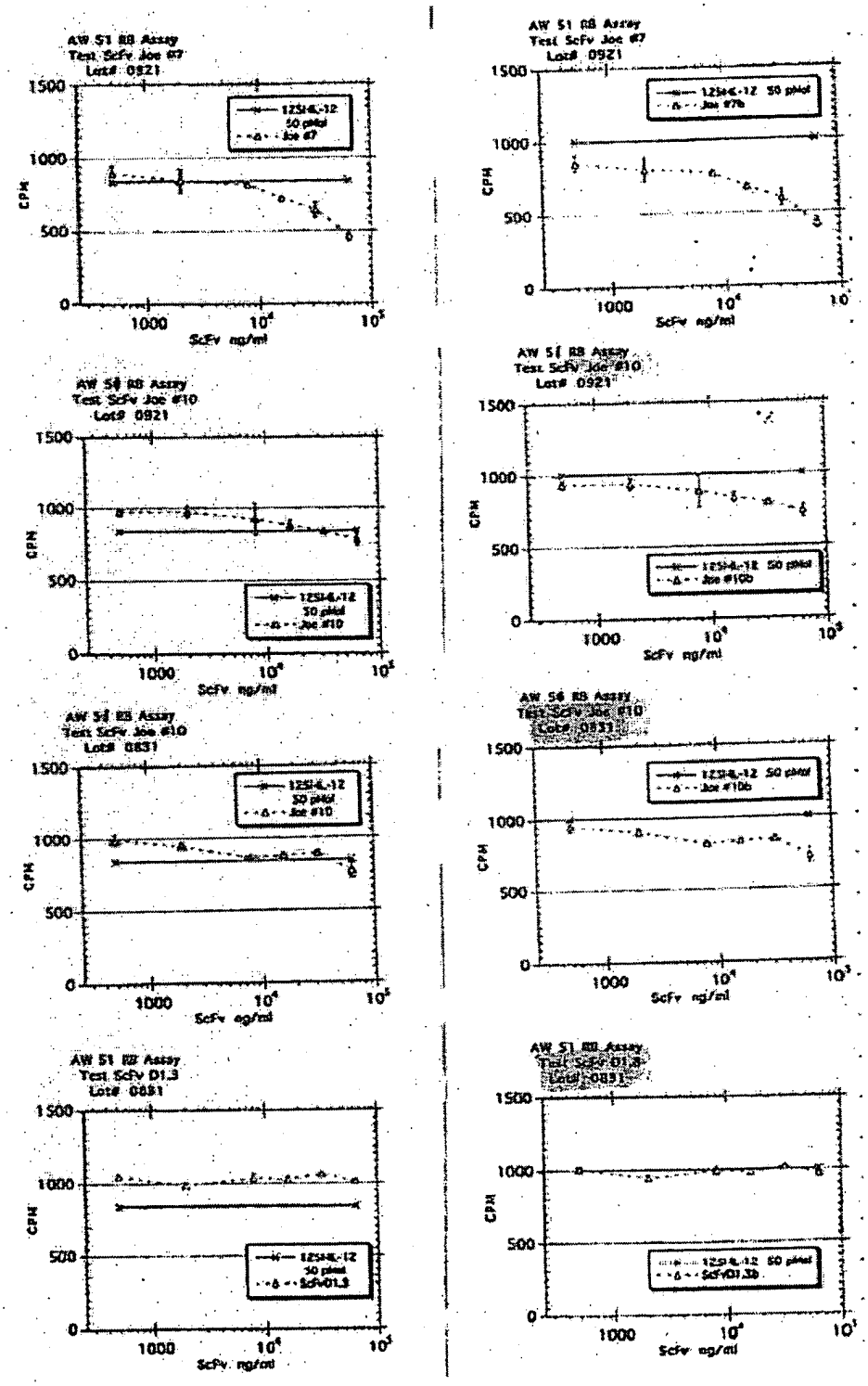
Ex 1329, ¶ 35; Ex 1345, page 107 (top right corner). See also Abbott Admitted Fact 134 (page 47).

After experiments with Joe 10 scFv antibody, Widom also wrote on page 108 of her laboratory notebook 4621:

Joe #10 is
also some how
neutralizing
to at [sic—a] less extent
than Joe 7
~ 7% - 26%
both lots
0921 & 0831

Ex 1329, ¶ 35; Ex 1345, page 108, right side.

On 26 September 1995, Widom understood Joe 7 and Joe 10 scFv antibodies bound to human IL-12 and neutralized human IL-12 binding by at least 20% and not less than 10%. Ex 1329, ¶ 36. The percentage of inhibition was also recognized as being "dose dependent." *See* (1) Ex 1345, page 108, top right ["and it is dose dependent"] and (2) the downward slopes of the curves in the Joe 7 and Joe 10 graphs on page 108 where CPM [counts per million] decreases as a function of concentration [dose—"ng/ml"] vis-à-vis the level curves on the two graphs at the bottom of page 108.



Graph 11

Graph 11 depicts eight graphs from page 108 of Widom notebook 4621

Widom discussed with Veldman the results of the RBA Assay that she obtained on about 26 September 1995. Admitted Abbott Fact 137 (page 48); Ex 1329, ¶ 37.

On or about 15 November 1995, Widom evaluated the ability of antibodies Joe 20 and Joe 22 to human IL-12 to neutralize radiolabelled human IL-12. Ex 1329, ¶ 38; Ex 1346.

Widom used PHA blast cells "PHA TV1600-C." The cells were obtained from Veldman. The results of the evaluation are recorded on pages 26-33 of Widom laboratory notebook 4746 [Ex 1346]. Admitted Abbott Fact 139 (page 48); Ex 1329, ¶ 39.

Veldman gave Widom the scFvs Joe 20 and Joe 22 when they were received from GI. Admitted Abbott Fact 140 (page 48); Ex 1329, ¶ 40.

Widom analyzed the ability of the antibody scFvs Joe 20 and Joe 22 to inhibit binding of radiolabelled IL-12 to IL-12 receptors on PHA blasts. Admitted Abbott Fact 141 (page 49); Ex 1329, ¶ 42.

Widom prepared graphs of tests of antibody scFv Joe 20 and Joe 22 to PHA blast stimulated IL-12 receptors. Ex 1329, ¶ 45.

The graphs appear on page 32 of Widom's laboratory notebook 4746 [Ex 1346]. Widom plotted the counts (CPM) on the Y axis and the antibody scFv concentrations in moles (M) on the abscissa. Ex 1329, ¶ 46; Ex 1346.

The graph [**Graph 3**, *supra*] shows the CPM of PHA stimulated blast cells where ^{125}I-IL-12 was bound as a line designated by "X," corresponding to the non-specific binding subtracted counts summarized at pages 30-31 of Notebook 4746. Admitted Abbott Fact 144 (page 49); Ex 1329 ¶ 47.

Graph 3 shows the CPM of PHA stimulated blast cells where ^{125}I-IL-12 was not bound to the IL-12 receptors present on the surface of the PHA stimulated blast cells as a hatched line with circles corresponding to the non-

specific binding subtracted counts summarized at pages 30-31 of Widom laboratory notebook 4746 [Ex 1346]. Centocor response to Abbott Fact 145 (page 49).

The downward slope of the hatched line with circles (CPM of PHA stimulated blast cells) in **Graph 4**, *supra*, versus the line having the designation "X" represents increasing neutralization with higher concentrations of antibody. Ex 1329, ¶ 47.

Graph 4 affixed to page 32 of Widom laboratory notebook 4746 [Ex 1346] shows the CPM of PHA stimulated blast cells where ^{125}I-IL-12 was bound as a line designated as "X", corresponding to the non-specific binding subtracted counts summarized at pages 30-31 of Widom laboratory notebook 4746 [Ex 1346]. Admitted Abbott Fact 147 (page 50); Ex 1329, ¶ 48.

Graph 4 also shows the CPM of PHA stimulated blast cells where ^{125}I-IL-12 was not bound to the IL-12 receptors present on the surface of the PHA stimulated blast cells. In Widom's opinion, non-binding was due to neutralization of the IL-12 by antibody scFv Joe 22. Ex 1329, ¶ 48.

The downward slope of the hatched line with circles (CPM of PHA stimulated blast cells) in **Graph 4** versus the line having the designation "X" represents increasing neutralization with higher concentrations of antibody. Ex 1329, ¶ 48.

On 16 November 1995, Widom obtained the results from an RBA started 15 November 1995. Admitted Abbott Fact 150 (page 51); Ex 1329, ¶ 49.

Widom recorded the results on pages 31-32 of her laboratory notebook 4746 [Ex 1346]. Admitted Abbott fact 151 (page 51); Ex 1329, ¶ 49.

Widom showed that the Joe 20 scFv antibody neutralized the binding of radiolabelled human IL-12 by 49.7%. Ex 1329 ¶ 49.

Widom also showed that the Joe 22 scFv antibodies neutralized the binding of radiolabelled human IL-12 by 53.5%. Ex 1329, ¶ 49.

On 16 November 1995, Widom discussed with Veldman the results of the RBA Assay that she obtained earlier that day. Admitted Abbott Fact 154 (page 51).

On 16 November 1995, Widom understood on that the isolated Joe 20 and Joe 22 scFv antibodies bound to human IL-12 and neutralized human IL-12. Ex 1329, ¶ 50. Centocor denies Abbott Fact 155 presumably because Centocor does not believe Widom "contemporaneously" recognized neutralization. Overlooked by Centocor is the following appearing on page 32 of Widom laboratory notebook 4746:

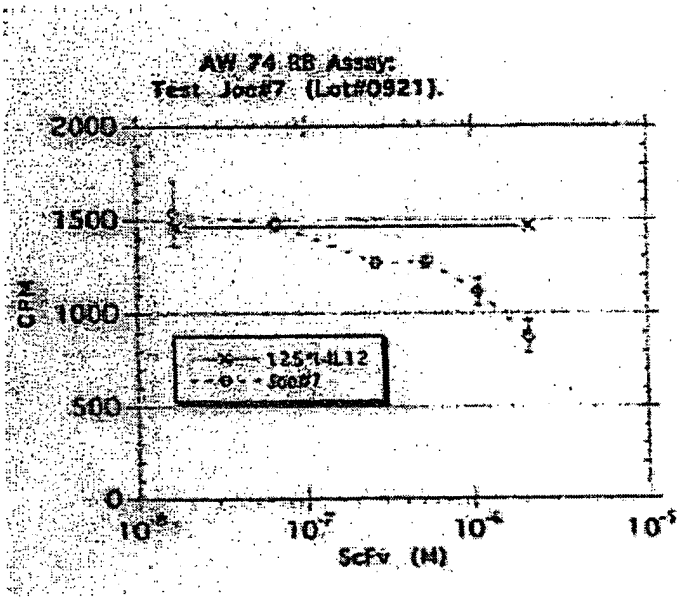
> Results
> Great Both Joe #20 & Joe #22 are Neutralizing
> The % of neutralization is better than our positive control = Joe #7
> Our negative control gives 0 neutralization

On or about 15 November 1995, Widom had repeated experiments using Joe 7. Admitted Abbott Fact 156 (page 52); Ex 1329, ¶ 51.

Widom recorded the results of the experiment she began on 15 November 1995 on pages 31-32 of her laboratory notebook 4746 [Ex 1346}. Admitted Abbott Fact 157 (page 52); Ex 1329, ¶ 51.

Based on her 15 November 1995 experiments with Joe 7 scFv antibody, Widom believed that at an appropriate concentration Joe 7 neutralized the binding of radiolabelled human IL-12 by 40.18%. Ex 1329, ¶ 52; Ex 1346, page 31, column ¾ down the page identified as Joe #7 inh

[where "inh" means inhibition]. Widom's beliefs are consistent with her graph of results of testing with Joe 7. The graph is set out below.



Graph 12

Graph 12 depicts Widom testing of Joe 7 on 15 November 1995

Widom again understood on 16 November 1995 that Joe 7 scFv antibody bound to human IL-12 and neutralized human IL-12. Widom's 16 November 1995 understanding is consistent with her previous similar understanding of 19 September 1995. Ex 1329, ¶ 52-53. Also compare **Graph 12** (AW 74 RB Assay) with the top left graph of **Graph 11** (prior Joe 7 AW 51 RB Assay) where the curves appear to be similar.

The results of the RBA Assay that Widom conducted on or about 16 November 1995 were included in Milestone 2 Report dated 12 December 1995. Admitted Abbott Fact 160 (page 52). Ex 1365, § 7, pages 9/13; Ex 1329, ¶ 54.

Milestone 2 Report in Section 7 reports that the Joe 20 antibody exhibited 50% neutralization at 2 μM and that the Joe 22 antibody exhibited 50% neutralization at 2 μM. Admitted Abbott Fact 161 (page 53).

Three graphs from Widom's experiment recorded at pages 32 of her laboratory notebook 4746 (Ex 1346, page 32) were included in Milestone 2 Report. Admitted Abbott Fact 162 (page 53).

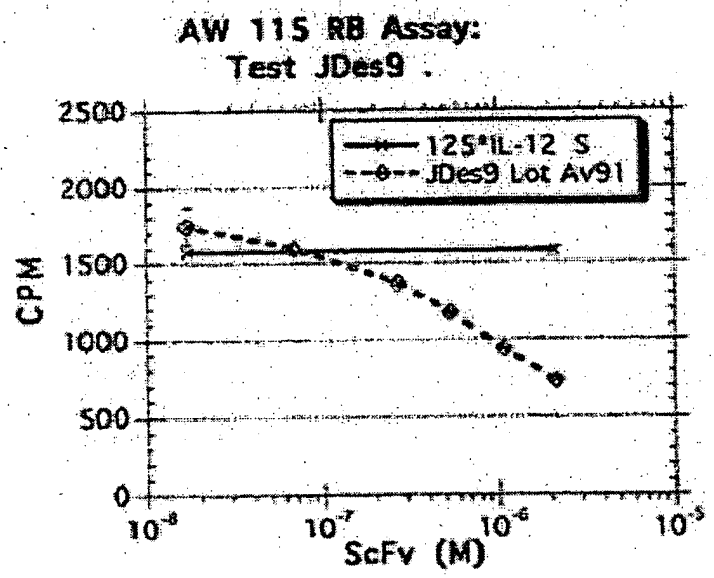
Beginning on or about 6 March 1996, Widom evaluated the ability of antibodies JDes9 to human IL-12 to neutralize radiolabelled human IL-12 binding to the IL-12 receptors present on the surface of PHA stimulated human blast cells in a RBA. Ex 1329, ¶ 56.

Widom laboratory notebook 4880 (Ex 1347) contains graphs produced by Widom as a result of her experimentation. Ex 1329, ¶ 58.

In making the graphs displayed on page 53 of experiment AW112, Widom plotted the counts (CPM) on the Y axis and the antibody scFv concentrations in moles (M) on the abscissa. Admitted Abbott Fact 164 (page 53).

As it turns out, Widom mistyped the experiment name on the two graphs on page 53 of her laboratory notebook 4880 [Ex 1347]. The names of the graphs on the left and right on page 53 should read "AW **112** RB Assay: Test Joe#20" [bold added; 112 replaces 115] and "AW 115 RB Assay: Test JDes9" respectively. Admitted Abbott Fact 165 (page 53).

The graph titled "AW 115 RB Assay: Test JDes 9" is reproduced below.



Graph 13

Graph 13 depicts results of Widom experiments with JDes9

Graph 13 shows the CPM of PHA stimulated blast cells where ^{125}I-IL-12 was bound as a line designated as "X", corresponding to the non-specific binding subtracted counts summarized at pages 53-54 of Widom laboratory notebook 4880 [Ex 1347]. Admitted Abbott Fact 167 (page 54).

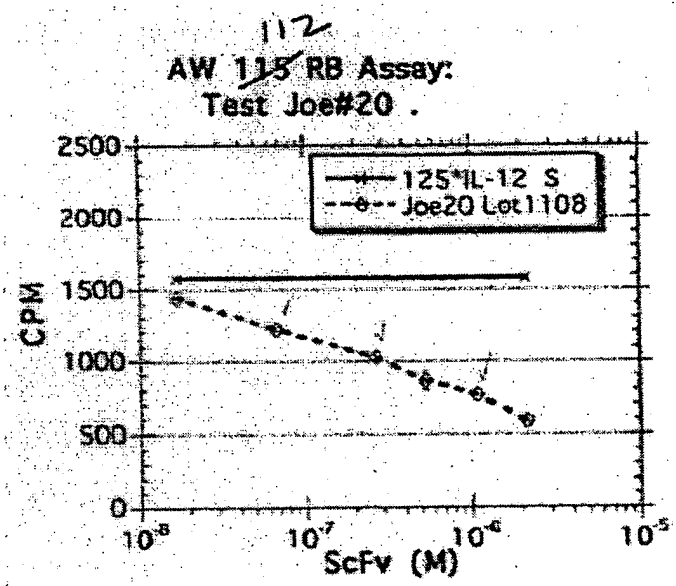
The downward slope of the hatched line with squares (CPM of PHA stimulated blast cells) of **Graph 13** versus the line having the designation "X" represents increasing neutralization with higher concentrations of antibody. Ex 1329, ¶ 65 [Widom direct].

On 13 March 1996, Widom obtained the results from the 6 March 1996 RBA. Admitted Abbott Fact 169 (page 54); Ex 1329, ¶ 66.

Widom found that at a particular concentration JDes 9 scFv antibody neutralized the binding of radiolabelled human IL-12 by 43.6%. Ex 1329,

¶ 66; Ex 1347, page 54 (see col. labeled "JDes9 % inh" ["inh" means inhibition]).

A graph prepared by Widom shows the results graphically and is reproduced below [the hand-written 112 corrects the typographical error discussed *supra*].



Graph 14

Graph 14 depicts results of Widom experiments with Joe 20

On 13 March 1996, Widom understood that the JDes 9 bound to human IL-12 and neutralized human IL-12. Ex 1329, ¶ 67.

On or about 6 March 1996, Widom repeated the experiment using Joe 20. Ex 1329, ¶ 68.

On 6 March 1996, Widom obtained the results from the RBA for the Joe 20 scFv antibody. Admitted Abbott Fact 173 (page 55).

Widom showed that at a particular concentration Joe 20 scFv antibody neutralized the binding of radiolabelled human IL-12 by 57.07%. Ex 1329, ¶ 69; Ex 1347, page 54 (col. labeled "Total binding Joe 20% inh ["inh" means inhibition]").

On or about 6 March 1996, Widom again understood that the Joe 20 scFv antibody bound to human IL-12 and neutralized human IL-12 binding. Ex 1329, ¶ 70.

On 13 March 1996, Widom discussed the results of the RBA Assay with Veldman. Admitted Abbott Fact 176 (page 55).

Widom further evaluated the ability of Joe 7 and JDes9 scFv antibody to neutralize radiolabelled human IL-12 binding to the IL-12 receptors present on the surface of PHA stimulated human blast cells in a RBA. Ex 1329. ¶ 72.

On or about 20 March 1996, Widom obtained the results of RBAs for the Joe 7 and JDes9 scFv antibodies. Admitted Abbott Fact 178 (page 56).

Widom was convinced that at a particular concentration the Joe 7 scFv antibody neutralized the binding of radiolabelled human IL-12 by 63.75%. Ex 1329, ¶ 73 (page 28:6); Ex 1348, page 92 (col. labeled "Joe7 % inh").

Widom was convinced that at a particular concentration the JDes9 neutralized by 59.11%. Ex 1329, ¶ 73 (page 28:7); Ex 1348, page 92 (col. labeled "JDes9 % inh").

Widom discussed with Veldman the results of the 20 March 1996 RBA Assay. Admitted Abbott Fact 180 (page 56).

On or about 20 March 1996, Widom again understood that the Joe 7 scFv antibody bound to human IL-12 and neutralized human IL-12. Her 20 March 1996 understanding confirmed her prior similar understandings of (1) 19 September 1995 and (2) 16 November 1995. Ex 1329, ¶ 74.

On or about 20 March 1996, Widom again understood that the JDes 9 scFv antibody bound to human IL-12 and neutralized human IL-12. Her

20 March 1996 understanding confirmed her prior similar understanding of 6 March 1996. Ex 1329, ¶ 74.

On or about 16 May 1996, Widom repeated the 6 March 1996 experiments using JDes9. Admitted Abbott Fact 183 (page 56).

On 18 May 1996, Widom obtained the results from the RBA for the "Joe 9" scFv antibody that she started 16 May 1996. Admitted Abbott Fact 185 (page 57).

As a result of the 16 May 1996 experiments, Widom was convinced that the Joe 9 scFv antibody neutralized the binding of radiolabelled human IL-12 at 51.76%. Ex 1329, ¶ 76; Ex 1349, page 17 [note that the "7" is missing from "17"], col. labeled Joe9 % inh.

On or about 18 May 1996, Widom discussed with Veldman the results of the 18 May 1996 RBA Assay. Ex 1329, ¶ 76.

On or about 18 May 1996, Widom understood that the Joe 9 scFv antibody bound to human IL-12 and neutralized human IL-12. Her 18 May 1996 understanding confirmed her prior similar understanding of 6 March 1996. Ex 1329, ¶ 77.

Venturini "work"

In 1995 and 1996, Venturini conducted experiments with human antibodies known as Joe 7, Joe 9, Joe 10, Joe 20, and Joe 22. Ex 1328, ¶ 9 [Venturini direct].

Venturini also repeated experiments with Joe 9, Joe 10, Joe 20, and Joe 22. Ex 1328, ¶ 9.

The object of the Venturini experiments was to evaluate the ability of human antibodies to human IL-12 to bind and neutralize human IL-12 by inhibiting the proliferation of PHA stimulated human blast cells. Ex 1328, ¶ 10.

The dates on which Venturini conducted experiments and the exhibit [laboratory notebook] in which experimental work is recorded is the following.

Exhibit # [Venturini laboratory notebook number]	Date	Joe number
Ex 1350 [4776]	5 December 1995	Joe 20 & Joe 22
Ex 1351 [4776]	6 December 1995	Joe 20 & Joe 22
Ex 1352 [4776]	18 January 1996	Joe 9 & Joe 10
Ex 1353 [4776]	24 January 1996	Joe 7
Ex 1354 [4476]	5 February 1996	Joe 7
Ex 1355 [4946]	2 April 1996	Joe 9

Venturini investigated the possibility of neutralization of human IL-12 by human antibody fragments to human IL-12 by exposing human IL-12 to the human IL-12 antibody fragments. Ex 1328, ¶ 10.

Venturini used a human PHA Assay, which utilized human peripheral blood mononuclear cells (called PBMC) isolated from freshly drawn, heparinized blood collected from a healthy donor by Ficoll-Paque gradient centrifugation. Admitted Abbott Fact 196 (page 59).

In performing the PHA Assay, Venturini followed a protocol described in Ex 1356 [for description of protocol see Appendix A at page 11-12]. Admitted Abbott Fact 197 (page 59); Ex 1328 ¶ 19.

We interrupt our discussion of Venturini's work to look into the GI protocol for verifying neutralization. More about Venturini's work later in the opinion.

Description of the GI protocol for verifying neutralization

The inhibition of specific IL-12-dependent proliferation by the scFv antibody is calculated by the following formula where CPM is counts per million:

$$\% \text{ Inhibition} = \left(1 - \frac{\text{CPM (with antibody)} - \text{CPM (background)}}{\text{CPM (without antibody)} - \text{CPM (background)}}\right) \times 100$$

Admitted Abbott Fact 198 (page 59); Ex 1328, ¶ 20.

The involved Centocor application indicates that any suitable test may be used to determine neutralization. Admitted Abbott Fact 200 (page 59).

The incorporation of (^{3}H)-Thymidine into cellular DNA of the PHA stimulated blast cells was measured by liquid scintillation counting. Admitted Abbott Fact 201 (page 60).

The incorporation of (^{3}H)-Thymidine into cellular DNA of the PHA stimulated blast cells was tabulated by using the non-specific binding subtracted counts. Admitted Abbott Fact 202 (page 60).

Graphs were generated where the counts (CPM) are plotted on the Y axis and the antibody scFv concentrations in ng/ml or moles (M) are plotted on the X-axis. Ex 1328 ¶ 21.

Numerous graphs of the kind mentioned by Venturini have been reproduced earlier in this opinion.

Inhibition or neutralization of human IL-12 is observed when the line (usually a hatched line with a square, circle or triangle) curves downward from left to right below the line corresponding to the specific binding counts (usually a straight line designated by "X"). Ex 1327--revised, ¶ 31 [Veldman direct]; Ex 1328, ¶ 21 [Venturini direct].

The downward slope of the hatched line with circles (CPM of PHA stimulated blast cells) versus the line having the designation "X" represents increasing neutralization with higher concentrations of antibody. Ex 1327, ¶ 31 [Veldman direct].

Back to Venturini's "work"

Beginning on or around 17 November 1995, Venturini became convinced that human antibodies designated as Joe 20 and Joe 22 bind to and neutralized human IL-12. Ex 1328, ¶ 22; Ex 1350.

Venturini obtained the PHA blast cells used in experiments described in Ex 1350 from Veldman. Admitted Abbott Fact 207 (page 61); Ex 1328, ¶ 23.

The graph entitled "AV64 PHA Blast Assay ScFv Inhibition of hIL-12" [**Graph 5**, *supra*] shows the CPM of (3H)-Thymidine incorporation into cellular DNA of the PHA stimulated blast cells. Admitted Abbott Fact 208 (page 61); Ex 1328, ¶ 28; Ex 1350, unnumbered page 4—following numbered page 3.

Graph 5 also shows neutralization activity of IL-20 activity by antibody scFv Joe 20. Ex 1328, ¶ 28 (page 12:1)

Graph 5 also shows neutralization of IL-12 activity by antibody scFv Joe 22. Ex 1328, ¶ 28 (page 12:4).

On or about 20 November 1995, Venturini obtained the results from the PHA Assays started about November 17, 1995. Admitted Abbott Fact 211 (page 61).

The last data point directed to Joe 20 in **Graph 5** represents a percent inhibition of cells of at least 20% and not less than 10%. Admitted Abbott Fact 212 (pages 61-62).

The last data point directed to Joe 22 in **Graph 5** represents a percent inhibition of cells of at least 20% and not less than 10%. Admitted Abbott Fact 213 (page 62).

Venturini noted her conclusion in the bottom right hand corner of the fourth page of her laboratory notebook [Ex 1350]. Venturini indicated "Conclude: 1. Joe 20, Joe 22 are both neutralizing ..." Admitted Abbott Fact 214 (page 62); Ex 1328, ¶ 29 (page 13:2).

By 5 December 1995, Venturini understood that the isolated Joe 20 antibody and the isolated Joe 22 human antibody bound to human IL-12 and IL-12-induced PHA blast cell proliferation. Admitted Abbott Fact 215 (page 62). Ex 1328 ¶ 30; EX 1350.

On 5 December 1995, Venturini discussed with Veldman the results of the 17 November 1995 PHA Assay. Admitted Abbott Fact 216 (page 62).

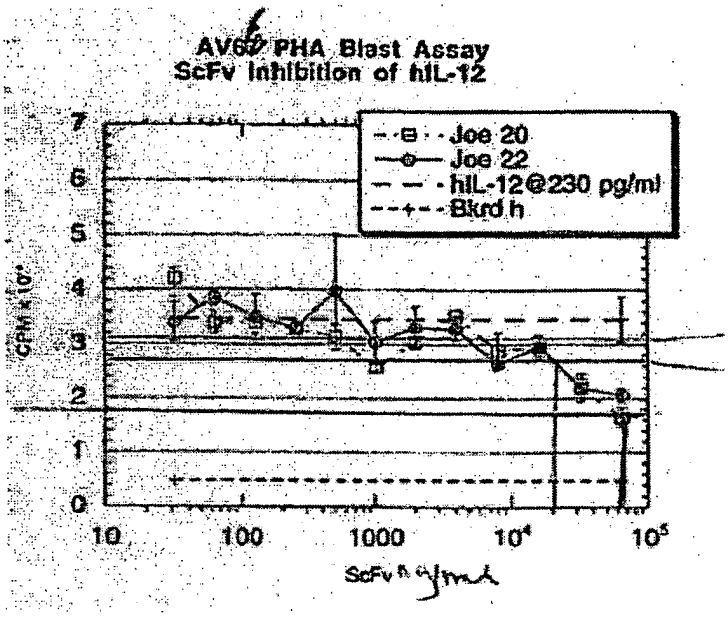
The results of the 17 November 1995 Venturini PHA blast assay experiments were included in Milestone Report 2 (12 December 1995). Admitted Abbott Fact 217 (page 62).

A graph [Ex 1365, page 10/13] similar to **Graph 5** from Venturini's laboratory notebook (Ex 1350, second graph from top on right hand side) is reproduced in Milestone 2 Report. Admitted Abbott Fact 218 (pages 62-63).

On or about 1 December 1995, Venturini conducted further PHA Assays using the Joe 20 and Joe 22 scFv antibodies. Based on those experiments, Venturini again concluded that Joe 20 and Joe 22 bound to and neutralized human IL-12. Ex 1328, ¶ 33.

On or about 4 December 1995, Venturini obtained the results from the 1 December 1995 PHA Assays. Admitted Abbott Fact 220 (page 63).

As a result of her experiments, Venturini generated a graph of data. The graph is reproduced below [AV66 PHA Blast Assay].



Graph 15

Graph 15 depicts results of Venturini experiments with Joe 20 and Joe 22

Data in **Graph 15** shows that the Joe 20 scFv antibody inhibited PHA blast proliferation by at least 20% and not less than 10%. Admitted Abbott fact 221 (page 63).

Data in **Graph 15** shows that the Joe 22 scFv antibody inhibited PHA blast proliferation by at least 20% and not less than 10%. Admitted Abbott fact 222 (page 63).

Venturini immediately shared the results of her **Graph 15** experiment with Veldman. Admitted Abbott Fact 223 (page 63).

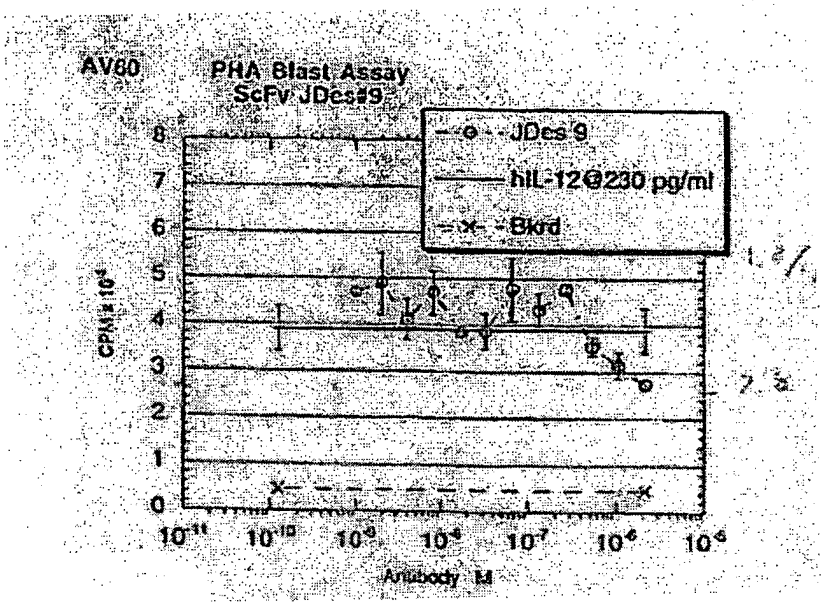
On or about 6 December 1995, Venturini understood that the isolated Joe 20 and Joe 22 human antibodies bound to human IL-12 and inhibited PHA stimulated human blast cell proliferation by at least 20% and not less than 10%,. Venturini's 6 December 1995 understanding confirmed her prior similar understanding of 20 November 1995. Ex 1328, ¶ 35.

Beginning on about January 12, 1996, Venturini conducted additional experiments to look into whether scFv antibody JDes9 and full length Joe 10 in COS conditioned media ("CM") would bind to IL-12 and to neutralize and inhibit the proliferation of PHA stimulated human blast cells. Ex 1328, ¶ 36

Venturini's 12 January 1996 experiments (1) are reflected in her laboratory notebook (Ex 1352) and (2) used PHA blast cells obtained from Veldman. Admitted Abbot Fact 227 (page 64); Ex 1328 ¶ 37.

"JDes 9" was originally designated "Joe 9." Admitted Abbott Fact 228 (page 64); Ex 1328, ¶ 37.

Some data resulting from Venturini's 12 January 1996 JDes 9 experiments are shown in the graph reproduced below. Ex 1352, page 81.

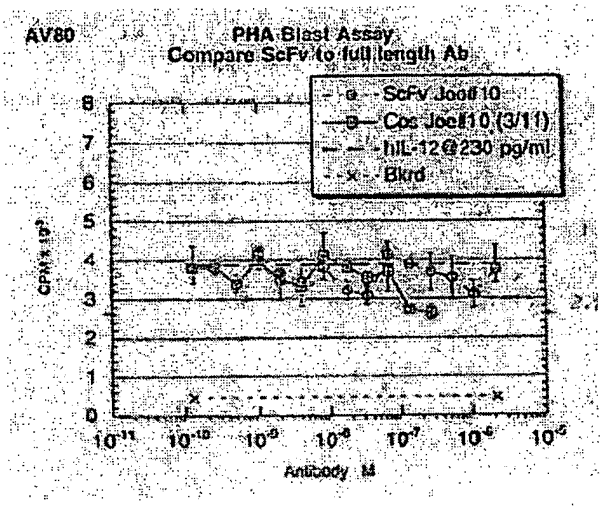


Graph 16

Graph 16 depicts results of Venturini experiments with JDes9

Graph 16 shows that at certain concentrations less proliferation of the blast cells is observed in the presence of scFv JDes9. Ex 1328, ¶ 42.

Some data resulting from Venturini's 12 January 1996 Joe 10 experiments are shown in the graph reproduced below. Ex 1352, page 81.



Graph 17

Graph 17 depicts results of Venturini experiments with Joe 10

Graph 17 shows that less proliferation of the blast cells is observed in the presence of Joe 10 antibody. Ex 1328 ¶ 43; EX 1352.

On or about 15 January 1996, Venturini obtained the results from the 12 January 1996 PHA Blast Assays. Admitted Abbott Fact 231 (page 65); Ex 1328, ¶ 44.

The data on page 81 of Venturini laboratory notebook 4776 (Ex 1352) shows that the JDes 9 antibody inhibited PHA blast proliferation by at least 20%, and not less than 10% at a concentration of 64 µg/ml. Admitted Abbott Fact 232 (page 65).

Venturini made a notation next to the Graph 16 that the last data point for the curve representing JDes 9 was at 2.8 CPM and corresponded to 30% inhibition. Admitted Abbott Fact 233 (page 65).

The Joe 10 antibody used in the 12 January 1996 experiments inhibited PHA blast proliferation by at least 20% and not less than 10% at a concentration of 32 µg/ml. Admitted Abbott Fact 234 (page 65).

Venturini, regarding Joe 10, (1) made a notation next to **Graph 17** and (2) noted the 30% inhibition ("% Inhibition") in the lower right hand corner of page 81 of Ex 1352. Admitted Abbott Fact 235 (page 65); Ex 1328, ¶ 45; Ex 1352, page 81.

On or about 12-18 January 1996, Venturini understood that both the isolated JDes 9 human antibody and the isolated COS derived full length Joe 10 human antibody (1) bound to human IL-12 and (2) inhibited PHA stimulated human blast cell proliferation by at least 20% and not less than 10%. Admitted Abbott Fact 236 (page 66).

On or about 18 January 1996, Venturini discussed with Veldman the 18 January 2009 results of the PHA Assay. Admitted Abbott Fact 237 (page 66).

Beginning on about 19 January 1996, Venturini began an experiment to determine possible neutralization by the antibody variable region fragment (scFv) Joe 7 in a PHA Blast Assay. EX 1328, ¶ 48.

Venturini obtained antibody scFv Joe 7 used in the experiment reflected in her laboratory notebook 4776 (Ex 1353) from Veldman. Admitted Abbott Fact 240 (page 66).

Some data resulting from Venturini's 19 January 1996 Joe 10 experiments are shown in **Graph 10**, *supra*. Ex 1353, page 96.

Graph 10 shows that less proliferation of the blast cells was observed in the presence of scFv Joe 7. Ex 1328, ¶ 53

On 23 January 1996, Venturini obtained the results from the 19 January 1996 Joe 7 PHA Assay. Admitted Abbott Fact 243 (page 67).

Data on page 96 of Venturini laboratory notebook 4776 (Ex 1353) shows that the Joe 7 antibody inhibited PHA blast proliferation or

neutralized IL-12 with an IC_{50} value at a concentration of 2×10^{-6} M. Ex 1328, ¶ 54; Ex 1353, page 96.

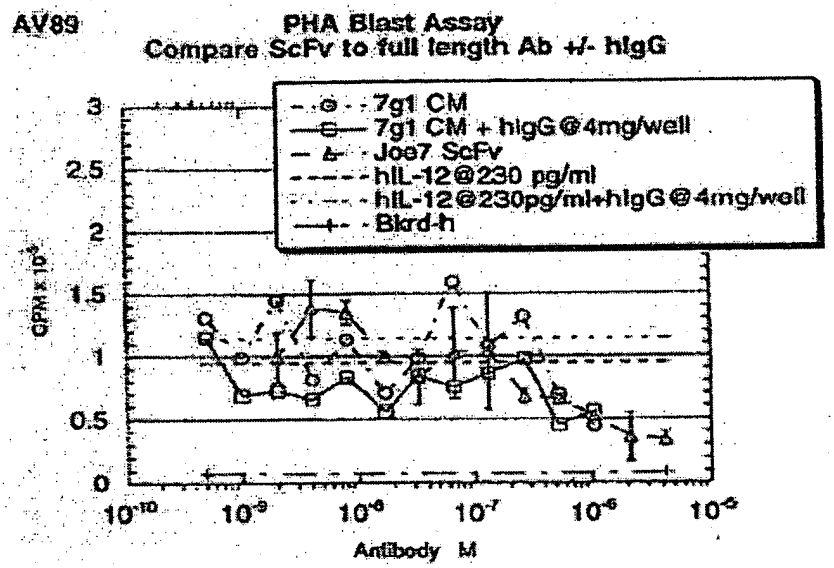
On 24 January 1996, Venturini understood that the isolated Joe 7 antibody bound and neutralized human IL-12 and inhibited PHA stimulated human blast cell proliferation by at least 20%, and not less than 10%. Ex 1328, ¶ 55.

Venturini discussed with Veldman the results of the PHA Assay that she obtained on 24 January 1996. Admitted Abbott Fact 246 (page 67).

Beginning on or about 2 February 1996, Venturini repeated experiments using the scFv Joe 7 antibody. Ex 1328, ¶ 57; Ex 1354 [laboratory notebook].

On or about 5 February 1996, Venturini obtained the results from the PHA Assay started on or about 2 February 1996. Admitted Abbott Fact 248 (pages 67-68).

Some data resulting from Venturini's 2 February 1996 Joe 7 experiments are shown in the graph reproduced below. Ex 1354, page 126.



Graph 18

Graph 18 depicts results from Venturini experiments with Joe 7

Graph 18 shows that the Joe 7 scFv antibody inhibited PHA blast proliferation with an IC_{50} value at a concentration of about 10^{-6} M. Admitted Abbott Fact 249 (page 68).

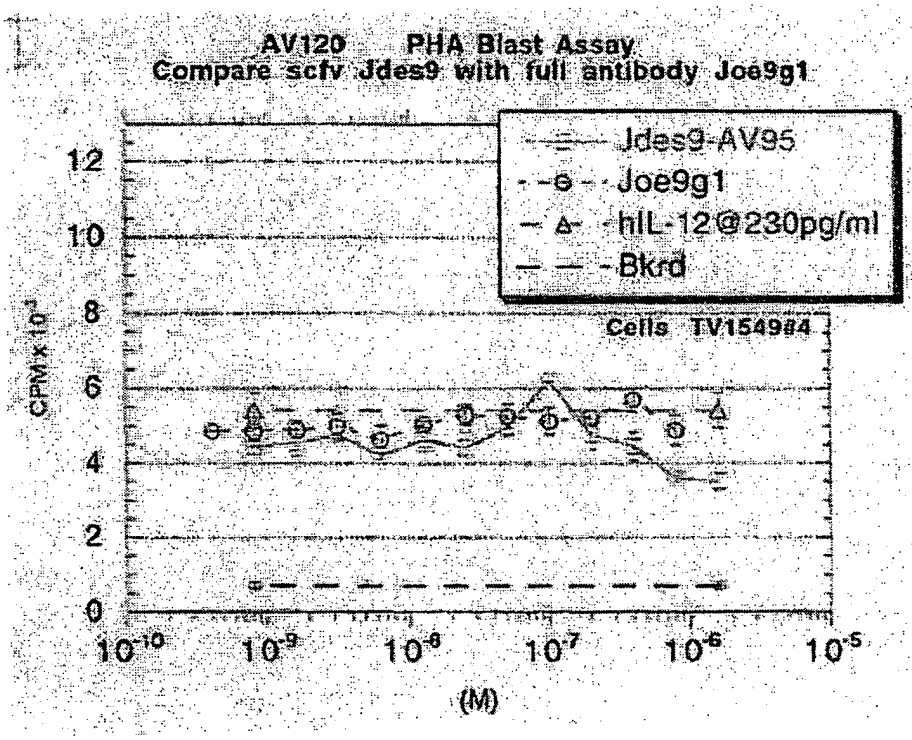
Venturini discussed with Veldman the results of the 5 February 1996 Joe 7 PHA Assay. Admitted Abbott Fact 250 (page 68).

On or about 5 February 1996, Venturini understood that the Joe 7 antibody bound to human IL-12 and inhibited PHA stimulated human blast cell proliferation by at least 20% and not less than 10%. Venturini's 5 February 1996 understanding confirmed her prior similar understanding of 24 January 1996. Admitted Abbott Fact 251 (page 68); Ex 1328, ¶ 60.

Beginning on or about 1 April 1996, Venturini repeated experiments using the scFv JDes9 antibody. Ex 1328, ¶ 61 [Venturini direct]; Ex 1355 [laboratory notebook].

On or About 4 April 1996, Venturini obtained the results from the 1 April 1996 JDes9 PHA Assay started about April 1, 1996 on or about April 4, 1996. Admitted Abbott Fact 253 (page 68).

Some data resulting from Venturini's 1 April 1996 JDes9 AV 95 experiments are shown in the graph reproduced below. Ex 1355, page 50.



Graph 19

Graph 19 depicts results of Venturini experiments with JDes 9 AV 95

Apparently, it was impossible to conclude at concentrations shown in **Graph 19** that full length Joe 9g1 "is neutralizing." Ex 1355, page 50 (handwritten note). We will note that apparently full length Joe 10gl did neutralize. *See* **Graph 7** and the discussion, supra, relating to Abbott Facts 95-96 and 99 (pages 38-40).

However, the last data point in **Graph 19** directed to JDes 9-AV 95 represents a percent inhibition of at least 20% and not less than 10%. Admitted Abbott Fact 254 (pages 68-69).

Venturini discussed with Veldman the results of the JDes9-AV95 PHA Assay. Admitted Abbott Fact 255 (page 69).

On or about 4 April 1996, Venturini understood that the isolated "JDes 9" antibody bound to human IL-12 and inhibited IL-12-induced PHA blast cell proliferation by at least 20% and not less than 10%. Venturini's 4 April 1996 understanding confirmed her prior 18 January 1996 similar understanding. Admitted Abbott fact 256 (page 69).

Corroboration by Nancy Wood

During May 1995 to May 1996, Veldman, Widom, and Wood worked at GI. GI (1) was a relatively small company at that time and (2) consisted of a single building. Admitted Abbott Fact 257 (page 69).

Wood was aware of, and familiar with, Widom's work conducting biological assays, including receptor binding assays (RBAs) using human antibodies. Admitted Abbott Fact 258 (page 69).

Wood was aware that Widom and Venturini were working with Veldman. Admitted Abbott Fact 259 (page 69).

During 1995 to 1996, Wood was in constant daily contact with Widom and Venturini. Admitted Abbott Fact 260 (page 70).

The information contained in pages 26-33 of Widom laboratory notebook 4746 (Ex 1346) was disclosed to Wood and understood by her on 11 January 1996, as reflected by her signature and the handwritten date appearing at the bottom of those pages. Admitted Abbott Fact 261 (page 70).

Based on Wood's (1) background, (2) research and familiarity with immunology, (3) using antibodies in various assays, (4) experience in biological assays, and (5) performing receptor binding assays and PHA blast assays, Wood understood the work described at pages 26-33 of Widom

laboratory notebook 4746 [Ex 1346] at the time Wood signed and dated Widom's laboratory notebook. Admitted Abbott Fact 262 (page 70).

During 1995 to 1996, it was the general GI practice (1) for laboratory notebooks to be assigned to each scientist, (2) for experiments to be recorded by the scientist in the laboratory notebook and (3) for the scientist to sign and date entries in the laboratory notebook. While Centocor denies this fact, the record as a whole—including the laboratory notebooks we have discussed above along with the testimony concerning those notebooks—more than supports Abbott Fact 263 upon which this finding is based. *Cf.* Admitted Abbott Fact 61.

It was also the general GI practice for each page of the laboratory notebook to be signed and dated by a scientist that was not directly involved in the project and/or experiment described in a laboratory notebook. The purpose of signing was to attest to reading and understanding the experiment described and recorded in the laboratory notebook. While Centocor denies this finding, the Wood testimony says otherwise. *See, e.g.*, Ex 1330, ¶ 9.

In 1995 to 1996, Wood understood that Widom was conducting experiments to obtain isolated human antibodies that neutralized human IL-12. Ex 1330, ¶ 10.

Corroboration by Kathy Tomkinson

From 1995 to 1996, Tomkinson was aware of, and familiar with, Venturini's work conducting biological assays to determine the ability of human antibodies to bind to human IL-12 and neutralize it. Ex 1331, ¶ 5 [Tomkinson direct].

Venturini and Tomkinson were both in what Tomkinson calls the MBGE Group, and worked side-by-side—meaning that they were in the same laboratory bay or workbench and had lab benches that were next to

each other. Venturini and Tomkinson interacted on a daily basis. Admitted Abbott Fact 267 (page 71); Ex 1331, ¶ 6.

Tomkinson had a personal interest in the research conducted by Veldman, Venturini and Widom because of her (1) previous experience expressing IL-12 and (2) attendance at Anti-IL-12 Human Antibody project meetings to follow the progress of their research. Admitted Abbott Fact 268 (page 71).

During the 1995 to 1996 time frame, Tomkinson was aware of the Anti-IL-12 Human Antibody project. She attended weekly group meetings where the status of the project and new developments were discussed by Veldman and Venturini. Admitted Abbott Fact 269 (page 72).

According to Tomkinson, during 1995 to 1996, there were about 20 scientists in the MBGE Group at GI. Further according to Tomkinson, usually about two scientists in a single instance—which we take to mean a single meeting—would share their research with the other scientists in the MBGE Group at the weekly meetings. Admitted Abbott Fact 270 (page 72).

The information contained in, and appearing at pages 1-4, of Venturini laboratory notebook 4776 [Ex 1350] was disclosed to, and understood by, Tomkinson on 31 January 1996, as reflected by her signature and handwritten date, which are set forth at the bottom of pages 1-4. Admitted Abbott Fact 271 (page 72).

The information contained in, and appearing at, pages 11-15 of Venturini laboratory notebook 4776 [Ex 1351] was disclosed to, and understood by, Tomkinson on 31 January 1996, as reflected by her signature and handwritten date, which are set forth on pages 11-15. Admitted Abbott Fact 272 (page 72).

The information contained in, and appearing at, pages 79-81 of Venturini laboratory notebook 4776 [Ex 1352], was disclosed to, and understood by, Tomkinson on 31 January 1996, as reflected by her signature and handwritten date, which are set forth on pages 79-81. Admitted Abbott Fact 273 (page 72).

The information contained in, and appearing at, pages 91-96 of Venturini laboratory notebook 4776 [Ex 1353] was disclosed to, and understood by, Tomkinson on 31 January 1996, as reflected by her signature and handwritten date, which are set forth on pages 91-96. Admitted Abbott Fact 274 (page 73).

The information contained in, and appearing at, pages 123-127 of Venturini laboratory notebook 4776 [Ex 1354] was disclosed to, and understood by, Tomkinson on 28 February 1996, as reflected by her signature and handwritten date, which are set forth on pages 123-127. Admitted Abbott Fact 275 (page 73).

The information contained in, and appearing at, pages 47-50 of Venturini laboratory notebook 4946 [Ex 1355] was disclosed to, and understood by, Tomkinson on 5 August 1996, as reflected by her signature which is set forth on those pages. Tomkinson recognized her signature and handwritten date on pages 47-50 of Venturini laboratory notebook 4946 [Ex 1355]. Admitted Abbott Fact 276 (page 73).

Based on her own research and familiarity with performing PHA blast assays, Tomkinson understood the work described on the pages of the Venturini laboratory notebooks mentioned above. Admitted Abbott Fact 277 (page 73).

In 1995 to 1996, Tomkinson understood that Venturini was conducting experiments to (1) obtain isolated human antibodies that bind to and (2) neutralize human IL-12. Ex 1331, ¶ 23.

Corroboration by Robert Gimlich

During May 1995 to May 1996, Robert Gimlich was generally aware of, the work conducted within the Veldman group, including the work of Widom. Admitted Abbott Fact 279 (page 74).

Gimlich's office was located close to Widom's office. Gimlich saw Widom daily. Admitted Abbott Fact 280 (page 74).

The information described and appearing at pages 82-90 of Widom laboratory notebook 4621 [Ex 1344] was disclosed to, and understood by, Gimlich on 11 January 1996, as reflected by his signature and the handwritten date, which are set forth on the bottom of those pages. Admitted Abbott Fact 281 (page 74).

The information described and appearing at pages 102-108 of Widom laboratory notebook 4621 [1345] was disclosed to, and understood by, Gimlich on 11 January 1996, as reflected by his signature and handwritten date, which are set forth on the bottom of those pages. Admitted Abbott Fact 282 (page 74).

Based on his (1) background, (2) research and (3) familiarity with immunoassays, Gimlich understood the work described in the Widom laboratory notebooks described above. Ex 1335, ¶¶ 7 & 9 [Gimlich direct].

In 1995 to 1996, Gimlich understood that Widom was screening for IL-12 neutralizing antibodies. Ex 1335, ¶ 11.

Corroboration by Beatriz Carreno

Carreno was familiar with the research conducted being conducted by Widom at GI during 1995 and 1996. Admitted Abbott Fact 285 (page 75).

According to Carreno, Widom and Carreno frequently discussed various experimental assays useful for determining biological neutralization, including PHA blast proliferation cell assay and receptor binding assay. Ex 1332, ¶ 6 [Carreno direct].

During 1995 to 1996, it had been the GI practice for GI scientists to give a presentation sharing their work with the other scientists at GI once or twice a year. Admitted Abbott fact 288 (page 75).

At one of these meetings during 1995 or 1996, Carreno recalls Veldman giving a presentation on the Anti-IL-12 Human Antibody project. Carreno remembers that Veldman was the project leader. Admitted Abbott Fact 289 (page 76).

Carreno recalls that during the presentation, Veldman discussed the research that was being conducted at GI on accomplishing a human antibody to human IL-12. Admitted Abbott Fact 290 (page 76).

Carreno recalls that Veldman discussed the biological data and bioassay analysis work being conducted by Widom and Venturini. Specifically Carreno says she recalls the PHA blast proliferation neutralization assay and receptor binding assay work being conducted pursuant to the collaboration that Carreno further recalls existed at that time between GI, BASF and CAT. EX 1332, ¶ 7.

Carreno also recalls that the antibodies that were the subject of the experiments being conducted by Veldman, Widom and Venturini were obtained from human scFv libraries developed at CAT. Admitted Abbott Fact 292 (page 76).

Carreno recalls that Widom was engaged in conducting receptor binding assays using human IL-12 antigen and human antibodies to determine the inhibition of IL-12 binding and activity. Admitted Abbott Fact 293 (page 76).

The information contained in, and appearing, on pages 14-19 of Widom laboratory notebook 5009 [Ex 1349], was disclosed to, and understood by, Carreno on 26 August 1996, as reflected by her signature and handwritten date, which are set forth at the bottom of these pages. Admitted Abbott Fact 294 (page 77).

Carreno understood that Widom conducted the experiments depicted in Widom laboratory notebook 5009 [Ex 1349]. Carreno understood that experiments show that human antibody bound to human IL-12 and neutralized human IL-12. Ex 1332, ¶ 12 [Carreno direct].

Activities at CAT

During 1995 and 1996 various relevant activities took place.

Elvin "work" and Duncan "work"

During 1995 and 1996, CAT was a small company. Admitted Abbott Fact 296 (page 77).

Elvin interacted with Duncan. Duncan was the Project Leader of the human IL-12 antibody project at CAT. At least during the period of 1995 to 1996, Elvin interacted with Duncan almost on a daily basis to obtain human antibodies that bind to human IL-12. Abbott Admitted Fact 297 (page 77).

During at least the period of 1995 to 1996, Duncan and Elvin reviewed each others' laboratory notes and communicated on a routine basis. Abbott Admitted Fact 298 (page 77).

Milestone 2 Report [Ex 1365, Section 8] states:

2 lineages of human anti-hu IL-12 antibody fragments with ≥ 10% IL-12 neutralization activity in an assay agreed by all parties, and also reports that the human antibodies obtained exhibited inhibition of 40, 50, and 50% (Joe 7, Joe 20, and Joe 22) as evidenced by the table in Section 7 on page 7.

Admitted Abbott Fact 299 (page 78).

Duncan received the human IL-12 from GI and gave them to Elvin for use in experiments using ELISA [enzyme-linked ImmunoSorbent Assay]. Admitted Abbott Fact 300 (page 78).

Elvin was a Senior Research Scientist on the human IL-12 antibody project. Elvin was responsible for (1) selecting human IL-12 antibodies from large human scFv phage display libraries, (2) analyzing antibodies for specificity, (3) sequencing antibodies and (4) establishing antibody lineages. Admitted Abbott Fact 301 (page 78).

Elvin used human scFv phage display libraries in the human IL-12 antibody project to select for human antibodies to human IL-12. Admitted Abbott Fact 302 (page 78).

The human scFv phage display antibody libraries Elvin used in order to obtain the human antibodies to human IL-12 were created by Vaughan. The libraries were sometimes called (1) VOGON I and VOGON II or (2) "scFv Library 1" and "scFv Library 2" or (3) "scFv 1" and "scFv 2", respectively. Admitted Abbott Fact 303 (pages 78-79). VOGON refers to Vaughan. Ex 2071, page 33:16-21

The technical details of creating the library are described in Ex 1364. *See* Ex 2071, page 15:2-13 (Vaughan cross). Our understanding of a "library" is the following. A biotech library is a highly useful biotech tool and is essentially a group of compounds—like books on a library shelf. The

compounds (e.g., antigens) in the library can then be used to see if one (or several compounds) will, for example, bind to other compounds (e.g., antibodies). The compounds which bind can then be further investigated; those that do not bind can be rejected for further experimentation. The Vaughan library was quite large and may have as many as 10^{11} variants. Ex 2069, page 17:3-5.

The human scFv libraries contained many pieces of human antibody genes encoding the many antigen-binding (called variable V) domains of human antibodies that are fused to phage genes encoding a surface coat protein of a bacteriophage. Admitted Abbott Fact 304 (page 79).

The phage display libraries developed by Vaughan consisted of bacteriophage containing human antibodies, a small fraction of which were specific to human IL-12 and the bacteriophage proteins including a coat protein, and the phage coat protein and human antibody protein were fused. Admitted Abbott Fact 305 (page 79).

The large bacteriophage libraries were incubated with human IL-12 that Elvin obtained from GI and non-bound bacteriophage were washed away, and specifically bound antibodies remained. Admitted Abbott Fact 306 (page 79).

Activities between 1996 and 1999

Centocor maintains that if Abbott actually reduced to practice, then Abbott suppressed or concealed the actual reduc
tion to practice. Why? According to Centocor, it took too long to file a patent application after the actual reduction to practice. Centocor therefore reasons that an inference of suppression or concealment is permissible. Abbott for its part denies any notion of having suppressed or concealed.

Instead, Abbott maintains that it was perfecting the invention. Abbott's factual basis is based largely on testimony of Kamen.

Kamen testimony

Kamen understands that Abbott Patent 6,914,128 is involved in this interference. Ex 1321—revised, ¶ 1.

From June 1991 to April 2002, Kamen was President of BASF, now Abbott BioResearch Center (hereinafter Abbott). Ex 1321—revised, ¶ 3.

In his testimony, Kamen refers to BASF as BBC. Ex 1321—revised, ¶ 3. However, for consistency in this opinion we will refer to BBC as BASF.

From about May 1993 to about March 1999, Kamen had overall responsibility for BASF. Ex 1321—revised, ¶ 3.

There came a time when it was decided to undertake an "Isolation of Human Antibodies which Neutralize Human IL-12" project, sometimes referred to as the "IL-12 antibody project."

The project was a collaboration between three companies: (1) BASF (now Abbott), (2) GI (now Wyeth) and (3) CAT (now MedImmune). Ex 1321—revised, ¶ 5 (Kamen direct); Ex 1358, page 4, ¶ 3.1 (Milestone 1 Report).

The three companies shared responsibilities for accomplishing human antibodies to human IL-12 which neutralize human IL-2. Ex 1321—revised, ¶ 5.

The project included at least (1) selection of IL-12 as a target, (2) evaluation and development of animal models for proof of concept, (3) affinity maturation and antibody expression, (4) human IL-12 production, (5) bioassay evaluation of candidate antibodies and (6) selection and affinity maturation of candidate antibodies that bind to human IL-12

using phage display technology. Ex 1321—revised, ¶ 5; Ex 1358, page 4, ¶ 3.2 and Appendix 7.

Selection of IL-12 as a target was accomplished by BASF under Kamen's supervision. Ex 2068, page 20:11-14 (Kamen cross-examination).

Kamen played a major role in selection of IL-12. Ex 2068, page 21:2-3.

As discussed earlier in this opinion, "milestones" were set for the project—meaning "objectives" to be achieved.

Milestone Reports were issued from time to time.

Kamen received a copy of Milestone 1 Report in his role as President of BASF. Ex 1321—revised, ¶ 5 (page 2:12)

Kamen recognizes Milestone 1 Report (Ex 1358) as a copy of a report identifying Duncan (CAT) and Elvin (CAT) as authors. Ex 1321—revised, ¶ 5.

In Kamen's opinion, Milestone 1 Report confirmed that the first milestone (objective) had been achieved. Ex 1321—revised, ¶ 5.

Kamen recognizes the handwriting on the cover letter dated 27 September 1995, as his handwriting. Ex 2068, page 25:6-8.

The handwriting authorizes payment of an invoice from CAT.

According to the Kamen testimony, the invoice "is also contained in Ex 1358." Ex 1321—revised, ¶ 5.

We have not been able to find the "invoice" but note that the cover letter (Ex 1358, page 1) states "I also enclose our invoice …."

The amount of the invoice on page 1 (as well as the entire second page of Ex 1358) is redacted.

The invoice and the amount of the invoice are not relevant to any issue before us.

Kamen believes that Ex 1358 is a true and accurate copy of Milestone 1 Report. Ex 1321—revised, ¶ 5.

During of 1993 to 1999, Kamen was familiar with the work Tracey, Salfeld, Banerjee related to the identification of new targets for the project. Ex 1321—revised, ¶ 6.

Kamen believes that (1) Elvin obtained human antibodies to the human IL-12 received from GI (2) used those antibodies in experiments and (3) found human antibodies that bound to the human IL-12.

Kamen's belief is consistent with § 4 of Milestone 1 Report. Ex 1321—revised, ¶ 13.

Kamen believes that scientists at BASF expressed human antibody fragments received from CAT for subsequent testing at GI.

Kamen further believes that Veldman and her team at GI used the expressed human antibody fragments from BASF to perform assays called receptor binding assays and PHA blast assays.

Kamen still further believes that the human antibodies Elvin identified neutralized human IL-12.

Kamen's belief is consistent with Milestone 2 Report which describes percent inhibition for Joe 7, Joe 20 and Joe 22 of 40%, 50% and 50%, respectively. Ex 1365 (Milestone 2 Report, page 9/13, § 7; Ex 1321—revised, ¶ 13.

According to Kamen, Milestone 2 Report (Ex 1365) is a copy of a report identifying as its authors Duncan and Elvin.

The report is attached to a cover letter dated 18 December 1995.

Kamen believes that Ex 1365 is a true and accurate copy of the 18 December 1995 cover letter and Milestone 2 Report. Ex 1321—revised, ¶ 13.

Milestone 3b Report dated 15 July 1996 (Ex 1402). The authors are identified, *inter alia*, as Elvin and Duncan.

Kamen would have received a copy of Milestone 3b Report. Ex 1321—revised, ¶ 14.

Kamen believes that Ex 1402 is a true and accurate copy of Milestone 3b Report.

In Kamen's view, Milestone 3b Report confirms that the third milestone (Milestone 3b) had been achieved. Ex 1321—revised, ¶ 14.

After 1995, Kamen understands that BASF, GI, and CAT collaborated to accomplish various Joe scFv antibodies with higher affinities to IL-12. The reader should know that we understand Kamen's ubiquitous use of "accomplish" or "accomplishment" to mean "achieved," "developed" or "completed." We continue to use Kamen's word in describing the rest of his testimony.

Kamen further understands that Ex 1304 is a true and accurate copy of the provisional application of the '128 Patent—provisional application 60/126,603.

Kamen still further understands that Ex 1430 is a true and accurate copy of the non-provisional application (09/534,717) that matured into the '128 Patent.

Kamen refers to the applications as (1) the provisional application and (2) the non-provisional application. During cross-examination, Kamen referred to the applications as a provisional and a final application. Ex 2068, page 16:18-19.

Kamen understands that there were continued efforts toward refinement of Joe 9.

We use the term understands, because Kamen did not personally participate in experimental work involving those continuing efforts. Ex 2068, page 38:16 to page 39:12.

Kamen further understands that those refinements are described in the specification and in Examples 1 and 2 of both the provisional and non-provisional applications. Ex 1321—revised, ¶ 14, page 7:5-7.

According to Kamen, Joe 9 scFv antibody was chosen for affinity maturation based on the Joe 9 exhibiting the lowest IC50 value in both the RBA and the PHA Assay, and based on Joe 9 having close to germline sequences. Ex 1321—revised, ¶ 14, page 7:7-9; Ex 2068, page 40:16-17. See also (1) Ex 1304, page 101:19-29 (provisional) and (2) Ex 1430, page 117:5-15 (non-provisional).

Once Joe 9 scFv was chosen for affinity maturation, Kamen understands that work continued at CAT to accomplish complimentary determining region 3 (CDR3) variants by site-directed mutagenesis using degenerate oligonucleotides specific for either the heavy chain CDR3 (H3) or the light chain CDR3 (L3). Ex 1321—revised, ¶ 14, page 7:12-14. See also (1) Ex 1304, page 101:30 to page 102:23 (provisional) and (2) Ex 1430, page 117:16 to page 118:11 (non-provisional).

Kaman believes that mutant clones were accomplished using biotinylated human IL-12 and checked by ELISA for human IL-12 binders, which were subsequently tested by BIAcore analysis to determine their rates (k_{off}). Ex 1321—revised, ¶ 14, page 7:16-18. See also (1) Ex 1304, page 102:24 to page 103:8 (provisional) and (2) Ex 1430, page 118:12-34 (non-provisional).

According to Kamen, details appearing in the provisional and non-provisional are described in greater detail in Milestone 3b Report (Ex 1402). Ex 1321—revised, ¶ 14, page 7:20 to page 8:1.

Kamen recognizes Ex 1402 as a copy of Milestone 3b Report. Ex 1321—revised, ¶ 14, page 8:3.

Kamen would have received a copy of the Milestone 3b Report. *Id.* at page 8:5.

In Kamen's view, Milestone 3b Report confirms to his satisfaction that Milestone 3b had been achieved.

Kamen believes that BIAcore analysis, which he believes was accomplished at CAT, identified several clones from the human antibody Joe 9 H3 and Joe 9 L3 libraries, including:

(1) clone 70/1 from the Joe 9 H3 library and

(2) clones 78-34 and 78-35 from the Joe 9 L3 library.

These clones are said to have exhibited a better k_{off} rate. See Ex 1402, Results—Heavy Chain Spike, § 6.2.1. See also (1) Ex 1304, page 103:9-22 (provisional) and (2) Ex 1430, page 118:35 to page 119:11 (non-provisional).

Kamen believes that clones 78-34 and 78-35 underwent neutralization assays, including RBA and PHA Assay by Veldman and her colleagues at GI. Ex 1321—revised, ¶15, page 8:15.

Kamen understands that clones 70/1 from the Joe 9 H3 library and clones 78-34 and 78-35 from the Joe 9 L3 library had the lowest IC_{50} values. Ex 1321—revised, ¶ 15, page 8:17. See also (1) Ex 1304, page 103:20-22 (provisional) and (2) Ex 1430, page 119:9-11 (non-provisional).

Kamen further understands that combination clones were accomplished by assembling the heavy chain mutants with the light chain

mutant together as scFv antibodies, and the k_{off} and IC_{50} values of the combination clones were also accomplished. Ex 1321—revised, ¶ 15, page 8:20. See also (1) Ex 1304, page 103:24-32 (provisional) and (2) Ex 1430, page 119:13-21 (non-provisional).

Kamen understands that clone 101-11 was selected for further affinity maturation, based on its k_{off} rate of 0.0045 s^{-1}. Ex 1321—revised, ¶ 15, page 9:3. See also Ex 1402, page 10, § 6.2.3—Joe 9 clones. Similar material appears in (1) Ex 1304, page 103:33 to page 104:2 (provisional) and (2) Ex 1430, page 119:22-28 (non-provisional).

Kamen understands that collaboration between BASF, CAT and GI continued after July 16, 1996, and through November 28, 1997.

Kamen further understands that as a result of continued collaboration, combination clone 101-11 was further affinity matured by CAT. Ex 1321—revised, ¶ 16, page 9:10-12. See also (1) Ex 1304, page 104:4-13 and Ex 1430, page 119:30 to page 120:2.

The mutant clones are believed by Kamen to have been accomplished with biotinylated IL-12; binding characteristics are believed to have been accomplished using BIAcore analysis, RBA, and PHA Assay. See (1) Ex 1403, page 104:7-9 (provisional) and (2) Ex 1430, page 119:33-35 (non-provisional).

Kamen understands that of the mutant clones accomplished, clone 103-14 exhibited an improved IC_{50} value and a low k_{off} rate. Ex 1321—revised, ¶ 16, page 9:17-18. See also (1) Ex 1304, page 104:11-13 and (2) Ex 1430, page 119:37 to page 120:22.

Kamen understands that clone 103-14 was selected for further affinity maturation, where four randomized libraries (H3 and L3.1,

L3.2, and L3.3) are believed to have been accomplished based on clone 103-14; the L3 of clone 103-14 was randomized in three different segments. Ex 1321—revised, ¶ 16, page 9:20 to page 10:3. See also (1) Ex1403, Milestone 4 Report, § 2, Generation and Selection of Randomized Libraries, (2) Ex 1304, page 104:15-28 (provisional) and (3) Ex 1430, page 120:4-17.

Kamen understands that at BASF and GI, mutant clones from the libraries were selected and screened by BIAcore to identify those with improved k_{off} rates. Ex 1321—revised, ¶ 16, page 10:5-9. See also (1) Ex 1304, page 104:28-30 (provisional) and (2) Ex 1430, page 120:17-19 (non-provisional).

Milestone 4 Report identifies as its authors at least Duncan and Elvin. Ex 1403.

Kamen would have received a copy of the Milestone 4 Report.

Kamen believes that Ex 1403 contains a true and accurate copy of the Milestone 4 Report. Ex 1321—revised, ¶ 16, page 10:17-20.

Based on what Kamen characterizes as a "tremendous effort" of screening libraries, clone Y61 was found and Y61 exhibited what Kamen believed to be an improved IC_{50} value. Ex 1321—revised, ¶ 16, page 10:9. See also Milestone 4 Report, E 1403, § 2, Generation and Selection of Randomized Libraries.

According to Milestone 4 Report, clone Y61, along with clone AO3, were identified as the two best clones. Ex 1403, § 2: "[i]t was from this effort that the two best clones Y61 and AO3 were identified." See also (1) Ex 1304, page 104:31-33 (provisional) and (2) Ex 1430, page 120:20-22.

Kamen understands that Y61 scFv antibody was converted to whole IgG1 and its binding characteristics were further measured. Ex 1321—revised, ¶ 16, page 10:12-13. See also (1) Ex 1304, page 104:33-38 (provisional) and (2) Ex 1430, page 120:22-27.

According to Kamen, clone Y61 is a fully human antibody. Ex 1321—revised, ¶ 16, page 10:15.

Further according to Kamen on or before 28 November 1997 it was determined that Y61 binds to and neutralizes human IL-12. Why the 28 November 1997 date? That is the date of Milestone 4 Report. In Kamen's view, Milestone 4 Report accepted Y61 as accomplishing a milestone. Ex 1321—revised, ¶ 16, page 11:1.

In Kamen's view, the fully human Y61 antibody is a refinement of the fully human Joe 9 antibody. To use Kamen's words, "[i]n other words, the Joe 9 antibody underwent affinity maturation and further development to accomplish Y61—which is itself fully human as a result of its Joe 9 lineage." Ex 1321—revised, ¶ 16, page 11:3-5.

Collaboration between BASF, CAT and GI continued after November 1997 and though [sic, through] at least August 26, 1998. Ex 1321—revised, ¶ 17.

During that collaboration, Kamen believes several different means to accomplish site-directed mutagenesis of single amino acid residues of the Y61 clone by BASF and GI, including mutagenesis of amino acids at direct contact positions, were accomplished. Ex 1321—revised, ¶ 17, page 11:7-9.

Potential antigenbinding amino acid residues in clone Y61 were targeted for further accomplishing the characteristics of Y61. Ex 1321—revised, 17, page 11:9-11. See also (1) Ex 1304,

page 105:29 to page 106:25 (provisional) and (2) Ex 1430, page 121:13 to page 122:14 (non-provisional).

Output clones were said to be accomplished for k_{off} rates using BIAcore and neutralization characteristics were accomplished using RBA and PHA Assay. Ex 1321—revised, ¶ 17, page 11:13-15. See (1) Ex 1304, page 106:26-29 (provisional) and Ex 1430, page 122:15-18.

Ex 1404 is recognized by Kamen as being a copy of the Milestone 5 Report dated August 26, 1998. The report identifies as its authors, *inter alia*, Duncan and Elvin. Ex 1321—revised, ¶ 17, page 12:5-8.

Kamen would have received a copy of the Milestone 5 Report and believes that Ex 1404 contains a true and accurate copy of the Milestone 5 Report. Ex 1321—revised, ¶ 17, page 12:7.

According to Kamen, the Milestone 5 Report confirms that the fifth milestone, or Milestone 5, had been achieved pursuant to the collaboration between BASF, CAT and GI. Ex 1321—revised, ¶ 17, page 12:9-10.

Analysis of the specific amino acid residue substitutions is said by Kamen to have revealed that at positions H52, L32 and L50, the substitution improved the k_{off} rates of Y61. Ex 1321—revised, ¶ 17, page 11:16 to page 12:2. See also (1) Ex 1404, "Results" (unnumbered pages 8-9, (2) Ex 1304, page 106:30-34 (provisional) and (3) Ex 1430, page 122:19-23 (non-provisional).

According to Kamen, combination clones of the output clones were accomplished at BASF, including the combination where Glycine was substituted with Tyrosine at L94 and L50. The substitution is said to have yielded a clone designated J695, which is further said to have accomplished a significant increase in neutralization ability. See

(1) Ex 1304, page 106:34 to page 107:8 and page 109:32-38 (provisional) and (2) Ex 1430, page 122:23-25 and page 125:24-30.

Starting on unnumbered page 3, Ex 1405 includes a "Development Committee Report to the Management Committee Meeting January 4, 1999."

The Report is accompanied by an Agenda (unnumbered page 2) and a Memorandum "From" Salfeld and Veldman *inter alia* to Kamen (unnumbered page 1).

Kamen believes that between 26 August 1998 (the date of Milestone 5 Report) and 24 March 1999 (the provisional application filing date), BASF continuing accomplishments included the development of a number of Chinese Hamster Ovary (CHO) cell lines expressing J695 for manufacturing of supplies to accomplish toxicology studies and formulation development for:

(1) pharmacology studies of J695 in cynomolgus monkeys,

(2) pharmacokinetics studies of J695 in mouse, rat, monkey and human serum matrix, and

(3) toxicology in cynomolgus monkeys.

Ex 1321—revised, ¶ 18, page 12:11-18.

Items (1) through (3) are discussed generally in the Development Committee Report (Ex 1405) at § IV (Pre-clinical Pharmacology), § V (Pre-clinical Pharmacokinetics) and § VI (Pre-clinical Toxicology). *See also* (1) Ex 1304, page 111:18-34 and page 113:30 to page 119:5 (provisional) and (2) Ex 1430, page 127:12-27 and page 129:31 to page 135:9 (non-provisional).

One purpose of development a number of Chinese Hamster Ovary cell lines was to move towards clinical trials of J695. Ex 2068, page 41:17 to page 42:25.

BASF had a "Patent Committee" and Kamen was a member of the committee. Ex 2068, page 19:9-15.

By 21 December 1998, Kamen was aware that a draft of the application that would become the provisional application had been prepared. Kamen understands that the draft was being reviewed by the involved companies, viz., BASF, GI and CAT. Ex 1321—revised, ¶ 19, page 13:5-8. See also § XI of Ex 1405:

> A patent application for J695 and the method used to generate the antibody will be filed before December 30, 1998. The patent draft has been reviewed by both companies [we believe both companies means BASF and GI] and in the final review stage. Any other intellectual property information will be discussed as appropriate.

It turns out that the 30 December 1998 proved to be somewhat optimistic given that the provisional was not filed under March 1999.

Based on his review of reports, it is Kamen's view that continuing efforts were made with respect to the IL-12 binding and neutralizing antibodies developed within the IL-12 project from about September 1995 through about March 1999.

Kamen's views are supported by contemporaneous documents, all of which Kamen would have received and would have relied upon as President of BASF. As Kamen points out, many

of the continuing efforts found their way into the Abbott provisional and non-provisional application.

5. Discussion

Issues

We decide the priority issues presented by the parties as set out in a motion, any opposition and any reply. *Cf. Brand v. Miller*, 487 F.3d 862 (Fed. Cir. 2007). We believe Abbott has told a "story" which is sufficiently credible to establish priority.

According to Abbott, conception by Salfeld, Banerjee and Tracey of the Centocor alternative of the count was "complete" no later than 30 July 1993. Paper 188, page 4:14. Centocor seems to agree. Admitted Abbott Fact 48 (pages 26-27). See also Paper 194, page 8:15-17.

The actual reduction to practice, on behalf of the three "inventors," was done in 1995-1996 through efforts of Elvin and Duncan (CAT) and Veldman, Widom and Venturini (GI). Centocor disagrees. Why?

Centocor Argument (1): Abbott is said not to have presented evidence of contemporaneous recognition by the inventors of the subject matter of the count that the invention of the count had actually been made. See, e.g., (1) Paper 194, page 4:7-8 and page 6:2-9.

Centocor Argument (2): The Abbott evidence concerning recognition of actual reduction to practice by "the other named inventors (the inventors not alleged to have contributed to conception of the subject matter of the Count)" is said to be legally insufficient because "they" ("the other named inventors") are not inventors of the subject matter of the Count. See, e.g., Paper 194, page 4:9-12 and page 6:10-18.

Centocor Argument (3): The Abbott evidence presented concerning recognition of actual reduction to practice by the other named

inventors is legally insufficient for the further reason that it is *nunc pro tunc*. Why? Centocor says Abbott relies on a definition of neutralization in Centocor's 1999 patent application which Abbott's inventors could not have known when they are alleged to have actually reduced the subject matter of the Count to practice in 1995. See, e.g., Paper 194, page 4:13-17 and page 6:19 through page 7:20.

Centocor Argument (4): Based on the length of time between any actual reduction to practice (1995-1996) and the filing of an Abbott provisional application (1999), an inference is raised that Abbott suppressed or concealed its actual reductions. In fact, says Centocor, Abbott has established that it was actually engaged in concealment of the invention. See, e.g., Paper 194, page 4:17 through page 5:4 and page 7:22 through page 8:8.

Comment about findings

In general, we have adopted many of the findings proposed by Abbott. Alternatively, we have adopted many of the Centocor responses to findings proposed by Abbott.

The Federal Circuit has observed that in *Anderson v. City of Bessemer, N.C.*, 470 U.S. 564, 572 (1985), the Supreme Court criticized the practice of "verbatim adoption of findings of fact prepared by prevailing parties, particular when those findings have taken the form of conclusory statements unsupported by citation to the record." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1374-75 (Fed. Cir. 1986). *See also Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1457 (Fed. Cir. 1984), which pre-dated *Anderson*.

Unlike the *Anderson* findings, Abbott's findings are supported by citations to the underlying evidence. We have considered the underlying

evidence cited. Centocor's responses to each of the Abbott findings have also been considered. Changes to the findings as proposed by Abbott have been made where we think it appropriate. Some of Abbott's proposed findings have not been adopted because we do not think they are controlling. All of the arguments on the merits of Abbott Motion 7 have been considered.

In light of the above, we assure the reader that the findings are ours and have been made after a review of the record.

Centocor argument (1)

Centocor argument (1) really is four arguments. The argument seemingly is bottomed on the proposition that Salfeld, Banerjee and Tracey are the "purported inventors" of the subject matter of the Count. Paper 194, page 6:3.

Centocor Argument (1-1): According to Centocor, there is no testimony from the "purported inventors" whether or when they considered the actual reduction of the subject matter of the count to have been completed. Paper 194, page 6:4-5.

Centocor Argument (1-2): According to Centocor, the record does not establish what meaning "they" attributed to the term "neutralization" according to the conception of the subject matter of the count. Paper 194, page 6:5-6.

Centocor Argument (1-3): According to Centocor, the record does not establish what tests "they" thought at the time were appropriate to test for neutralization. Paper 194, page 6:6-8.

Centocor Argument (1-4): Centocor asks: what test results would have satisfied "them" at the time that an antibody was neutralizing

according to whatever meaning "they" attributed to that term (i.e., "neutralizing). Paper 194, page 6:8-9.

Centocor Argument (1-1)

Abbott Motion 7 can be viewed as being somewhat unclear on the issue of who Abbott maintains conceived the invention. For example, Abbott states that scientists at BASF, "including" Salfeld, Banerjee and Tracey, worked together "to conceive of human antibody to human IL-12." Paper 188, page 3:7-10. When Centocor agreed that Salfeld, Banerjee and Tracey were the "conceivers," Abbott—no doubt surprised by Centocor's unexpected agreement—started what might be called a "retreat" the seed of which had actually been planted in the motion itself. The retreat involved stating the "conception of the subject matter of the Count occurred with *at least*" Salfeld, Banerjee and Tracey. Paper 238, page 7:9-10. Abbott goes on to say that "[n]owhere does Abbott allege that the only inventors of [the subject matter of] Count 1 are" Salfeld, Banerjee and Tracey. Paper 238, page 7:10-11.

At this point, Centocor truly can say "gotcha." Why? Look at what Abbott said in the first place. Abbott Motion 7 says that "Abbott's conception" was complete by 30 July 1995. Paper 188, page 4:14-15. Centocor, properly recognizing that juristic entity Abbott could not have conceived of anything, notes that the "Abbott" conceivers are Salfeld, Banerjee and Tracey. Paper 194, page 8:20-22.

As Centocor correctly noted at oral argument, a motion is supposed to put an opponent on notice of what it is that the opponent is opposing. A fair reading of Abbott Motion 7 reveals that Abbott is saying—whether Abbott wants to believe it or not—that Salfeld, Banerjee and Tracey are the inventors (conceivers) of the subject matter of Count 1. Even if we had

some doubt, we would agree with Centocor because the arguments in a motion are supposed to be clear. Centocor reasonably could assume Abbott was maintaining that Salfeld, Banerjee and Tracey "conceived" the invention of the count. It is on that basis that Centocor opposed and it is on that basis that we decide the motion. Abbott cannot plant a seed in a motion and expect thereafter harvest whatever crop it thinks appropriate as a case proceeds.

While Centocor prevails on the "who are the conceivers" skirmish, it looses overall on Centocor Argument (1-1). According to Centocor, there is no testimony from the "purported inventors" (now taken to be Salfeld, Banerjee and Tracey) whether or when they considered the actual reduction of the subject matter of the count to have been completed. On this point we disagree.

As noted in our findings, Venturini's November 1995 AV64 PHA Blast Assay for Joe 20 and Joe 22 [**Graph 5**] appears on page 10/13 of the December 1995 Milestone 2 Report. Milestone 2 Report was addressed to Salfeld. Ex 1365, page 1. Milestone 2 Report refers to percent inhibition based on a PHA Blast Assay for Joe 20 and Joe 22 of 28% and 40%. Ex 1365, page 10/13.

Venturini had previously conducted RBA's. Those too were reported via Milestone 2 Report to Salfeld. Ex 1365, page 9/13; Ex 1318, page 10:6. Prior to the November 1995 experiments, Veldman conducted September 1995 experiments. Via fax Veldman communicated her conclusions to Salfeld. Ex 1327—revised, ¶ 43; Ex 1373 ("As you can see the inhibition by Joe 7 (26% in [RBA] assay) in quite good."). To be sure as of September 1995, Veldman also said that "[n]one of the scFv's showed any inhibition in the PHA blast assay."

At the end of the day, Joe 20 and Joe 22 showed inhibition in the more significant PHA assays, all of which was reported to Salfeld. Milestone 2 Report reveals PHA assay inhibitions of Joe 20 and Joe 22 of 28% and 40%.

Based on Milestone reports of the work of Veldman, Widom and Venturini, a management decision was made by Kamen to permit the IL-12 project to continue.

Centocor Argument (1-2)

Centocor definitely has a problem with what meaning the personnel at BASF, GI and CAT attributed to "neutralization." Centocor reasons that the BASF, GI and CAT personnel could not have known about Centocor's definition of "neutralization" because that definition appeared (Centocor would say for the first time) in a Centocor application filed long after the supposed Abbott actual reductions to practice.

Abbott personnel often used the term "inhibition" rather than "neutralization." The tests conducted at GI and the conclusions reached by GI tests reveal two things. First, Veldman, Widom and Venturini had a test for determining neutralization. In fact, they had two tests: RBAs and PHAs. Second, contemporaneous laboratory notebooks and other communications establish that all three determined that a degree of neutralization took place and that the degree of neutralization was a function of concentration. In addition, it is manifest that to be sure they were not imagining a positive result, Veldman, Widom and Venturini took the wise course and checked and double-checked their results.

The results reported to Salfeld state that Joe 20 and Joe 22 had PHA assay inhibitions of 28% and 40%. Ex 1365, page 10/13. Salfeld went on to forward the results to others.

Based on language in the Venturini laboratory notebooks and the Milestone Reports, as well as the evidence as a whole, we are left with a definite conviction that when BASF, GI and CAT personnel used the term "inhibition" they meant what Centocor refers to as "neutralization." Section 7 of Milestone 1 Report shows, as Abbott maintains, that "neutralization" and "inhibition" were used as interchangeable words: "all neutralization assays were performed by ... Veldman and her colleagues at GE either by inhibition receptor binding or inhibition PHA blast proliferation." Ex 1365, § 7.

Centocor's argument that BASF, GI and CAT personnel could not have known about Centocor's "neutralizing" definition in 1995-1996 (because its application was not filed until 1999) is a side show apart from the main event. Milestone 2 Report shows a PHA assay inhibition for Joe 20 and Joe 22 of 28% and 40%. These two inhibition percentages fall squarely within the Centocor definition of "neutralizing" and the two inhibition percentages were determined by PHA assay long before Centocor filed its application.

Centocor arguments (1-3) and (1-4)

Centocor maintains that Abbott has failed to show what tests "they" thought were appropriate at the time (1995-1996) for establishing neutralization. Alternatively, Centocor asks what tests would have satisfied "them" according to "their" definition of neutralizing. The short answer is that Venturini ran inhibition receptor binding or PHA tests and as a result of those tests concluded that Joe 20 and Joe 22 were "neutralizing" (her word). Based on the work of Veldman, Widom and Venturini, we would be reluctant to find that "they" were not then aware of tests for verifying neutralization. It is probably true that at the end of the day, everyone at

BASF, GI and CAT settled on a definition of neutralizing based on PHA assays. Centocor's difficulty is that PHA assays showed GI inhibitions within the meaning of Centocor's definition in 1995. PHA results were communicated to Salfeld. Ex 1365.

Centocor argument (2)

Centocor takes the position that some of the individuals named as inventors on the involved Abbott patent "are not inventors of the subject matter of the Count." Paper 194, page 4:12.

We start with the proposition that inventorship is presumed to be correct. *Hamer v. White*, 31 CCPA 1186, 1191, 143 F.2d 987, 991 (CCPA 1944); *Brown v. Edeler*, 27 CCPA 1091, 1095, 110 F.2d 858, 861 (CCPA 1940) (both involving applications in interferences). See also *Seymour v. Osborne*, 11 Wall. (78 U.S.) 516, 553 (1870); *Acromed Corp. v. Sofamor Danek Group Inc.*, 253 F.3d 1371, 1379 (Fed. Cir. 2001) (both involving patents).

Conception is the touchstone of inventorship. *Stern v. Trustees of Columbia University in the City of New York*, 434 F.3d 1375, 1378 (Fed. Cir. 2006); *Scripps Research Institute v. Nemerson*, 72 USPQ2d 1122, 1122 (Bd. Pat. App. & Int. 2004).

Abbott and Centocor take the position, and in effect invite us to decide the case, on the basis of a conception by Salfeld, Banerjee and Tracey. We have accepted the invitation because that is the case presented to us. But, being an inventor of subject matter of a count is not the same as being an inventor named in a patent involved in an interference.

Centocor did not request, and was not authorized, to file a motion for judgment based on incorrect inventorship of the involved Abbott patent.

Accordingly, it should come as no surprise that there is no proof of who invented the subject matter of each of the claims in the Abbott patent. Therefore, Centocor is in no position to establish that Salfeld, Tracey and Banerjee are the only *joint* inventors of the subject matter *claimed in the involved Abbott patent.* To be sure, individuals other than Salfeld, Banerjee and Tracey are listed as inventors in the patent. However, as recognized by Centocor at oral argument, those other individuals may have contributed to aspects claimed in the Abbott patent beyond the subject matter of Count 1. *Cf. Stern v. Trustees of Columbia University*, 434 F.3d at 1378 (contribution to one claim is sufficient to be listed as a co-inventor).

Centocor Argument (3)

Centocor argues that the actual reduction to practice is *nunc pro tunc.* An actual reduction to practice cannot be established *nunc pro tunc. Langer v. Kaufman*, 59 CCPA 1261, 1265, 465 F.2d 915, 919 (CCPA 1972). The basis for Centocor's position is that the Abbott inventors of the subject matter of the count did not recognize, at the time (1995-1996), the definition of "neutralize" as it appears in Centocor's subsequent patent application.

Milestone 2 Report (Ex 1365, page 10/13) (1) is dated 18 December 1995, (2) addressed to Salfeld by Duncan (Ex 1365, page 10/13), (3) "would have [been] received" by Salfeld (Ex 1318, ¶ 21, page 10:12-13) and (4) has the following to say.

First, Milestone 2 was (Ex 1365, page 10/13) (italics added):

> 2 lineages of human anti-hu IL-12 antibody fragments with ≥10% neutralisation activity *in an assay agreed by all parties.* 1 lineage must bind to the p40 subunit and the other lineage must bind p70 in preference to p40.

Second, the conclusion expressed in Milestone 2 report (Ex 1365, page 10/13) was (italics added):

> Four different lineages have shown ≥10% neutralization in the receptor inhibition assay and two of these shows ≥10% *neutralization* in inhibition of PHA blast proliferation [i.e., Joe 20 and Joe 22 with inhibitions of 28% and 40%—data on the Venturini **Graph 5** experiments]. One of these lineages is a p40 specific binder, one binds p70>p40 and two appear to be p70 specific. None of these antibodies showed any binding to a panel of ten other antigens in an ELISA specificity assay. These lineages thus fulfill the requirements to meet Milestone 2.

Given that (1) Joe 20 and Joe 22 had AV64 PHA blast assay inhibitions of 28% and 40%, (2) Milestone 2 was "achieved" and (3) Salfeld would have received notice of the achievement, there is no *nunc pro tunc* reduction to practice.

Centocor Argument (4)

Centocor says BASF, GI and CAT suppressed or concealed the invention. Any suppression or concealment necessarily has to occur after an actual reduction to practice. We agree with Abbott that an actual reduction to practice took place sometime in 1995. Hence, in addressing Centocor Argument (4), we—like Centocor—assume an actual reduction to practice in the 1995 time frame.

Abbott did not get around to filing a provisional application until 1999. Based on an essentially three and one-half year delay, Centocor maintains that an inference of suppression or concealment is permissible.

We will assume Centocor is right—keeping in mind that Centocor, not Abbott, has the burden of proof on the suppression or concealment issue.

In a light most favorable to Centocor, and for the purpose of this case, we will shift the burden of going forward with the evidence to Abbott. Unfortunately for Centocor, Abbott has come forth with enough evidence to overcome any permissible inference of suppression or concealment.

After the 1995 actual reductions to practice, BASF, GI and CAT continued to investigate additional "Joes." Efforts to improve or perfect an invention after an actual reduction to practice can be permissible without running afoul of suppression or concealment. Kamen testified that, as President of BASF, he authorized—from a management point of view—continued effort on the Project. Why? Because he received favorable indications of progress via the Milestone Reports. After the 1995 actual reduction to practice of the Joe 20 and Joe 22 embodiments, numerous additional Joes are reported to have been tested, including Joe Y61. See, e.g., Milestone 4 Report. Ex 1403, § 2. In fact, according to Milestone 4 Report, Y61 was one of "the two best clones ...." *Id.* Based on what Kamen saw in the report, he believed Joe Y61 had an improved IC_{50} value. Ex 1321—revised, § 16, page 10:9. Y61 is described in both the Abbott provisional and Abbott non-provisional applications. In fact, most of the successful Joes—including Joe 20 and Joe 22—are described in the Abbott provisional and non-provisional application.

A further development reported to Kamen was clone—Joe J695. Development of Joe J695 is reported in Milestone 5 Report in August of 1998. Clone Joe J695 is also described in Abbott's provisional application and non-provisional application. It should be noted that Milestone 5 Report is dated after the assumed 30 April 1998 actual reduction to practice by the

Centocor inventors. Accordingly, Milestone 5 Report has not been considered to determine whether Abbott actually reduced to practice prior to Centocor. Rather, it is considered only as evidence offered by Abbott to overcome any adverse inference of suppression or concealment.

In our view *in this case,* continued development of the invention is consistent with a lack of legal suppression or concealment.

A more troubling aspect of the suppression or concealment matter is the timing of the filing of the Abbott provisional application. Why? According to Centocor, Abbott in effect sandbagged filing a patent application until Abbott was about ready to submit information to the FDA to enter clinical trials. We are not totally familiar with goings on associated with FDA sanctioned clinical trials. But, we are told by Centocor that once you submit information to the FDA, it becomes public. Abbott does not seem to deny this public nature of information submitted to the FDA.

Our understanding is that the invention could not be marketed for human use without FDA approval. We observe that as a general proposition there is nothing inherently evil about commercializing an invention. What might be considered evil is an entity regarding its commercial interests as being more important than the public interest in having invention disclosed via a patent application. If the commercial interest is regarded as more important, then delaying filing of an application can justifiably lead to a holding of suppression or concealment.

Kamen testified that he would have received Milestone 5 Report. Ex 1321—revised, ¶ 17, page 12:7. The report is dated 26 August 1998 and contains discussion about further testing of Joe Y61.

There came a time when a patent application was drafted. When work first began on the draft is not entirely clear. We do know that BASF had a

Patent Committee and that Kamen "was a member of that Patent Committee as head of the organization." Ex 2068, page 19:13-15 (Kamen cross). Kamen tells us that by 21 December 1998, he "was aware that a draft of the application that would become Abbott's involved provisional application had been prepared and was being reviewed by the involved companies." Ex 1321—revised, ¶ 19:5-8. We view the "was being reviewed by the involved companies" to mean "was supposed to be reviewed by the involved companies" since we are not sure Kamen has personal knowledge of what review was taking place at the involved companies. In any event, Kamen's 2008 testimony is generally consistent with contemporaneous 1998 documentation. Ex 1405, Part XI ("Patents")—in his declaration Kamen refers to the Arabic number 11 whereas the document uses the Roman number XI.

Ex 1405 also discusses Joe J695 which is said to have "benefited significantly" from previous research involving Joe Y61. See Part III.

One permissible inference is that once Joe J695 was developed, it was time to file a patent application. Another permissible inference is that Abbott delayed filing an application until information was about to be filed with the FDA.

Judge Terence T. Evans, writing for the Seventh Circuit, recently observed that "Trial judges sometimes find themselves between a rock and hard place." *United States v. Berry*, 565 F.3d 385, 386 (7th Cir. 2009). To some extent and in this case, we feel like we are between a rock and a hard place. When that happens, we (1) put on our impartial adjudicator hats, (2) determine who has the burden to proof and (3) resolve whether that burden been sustained.

In this case, under established precedent, Centocor has the burden of proving suppression or concealment. If a delay between an actual reduction to practice and filing an application is long enough, then the burden of going forward with the evidence on suppression and concealment "shifts" to the party maintaining that there is no suppression or concealment. The delay in this case, consistent with precedent, was long enough to permissibly shift to Abbott the burden of going forward. However, Abbott has a "story." After its 1995 actual reduction to practice, it continued research to perfect and/or improve the invention. The evidence reports development of various post-actual reduction to practice "Joes" (e.g., Joe Y61 and Joe J695) which are said to have properties which are better than those of the 1995 actual reduction to practice of Joe 20 and Joe 22. After Joe J695 was reported (e.g., Ex 1404, Milestone 5 Report—August 1998) and a determination was a patent should be filed to cover Joe J695 (Ex 1405, § XI—December 1998), a provisional application was thereafter filed in March 1999. When any submission to the FDA was made it is not entirely clear; also not clear is the nature of any submission. We assume any submission was after March 1999, but we are not sure when.

Back to the overall burden of proof—which falls on Centocor. When we balance the "inference" delay evidence with the Abbott "story," we hold that Centocor has failed to sustain its burden. Is this a close case? Yes. On this record, both the Abbott and Centocor positions are plausible. At the end of the day, we think the Abbott position more plausible—albeit just slightly more plausible—than the Centocor position. We therefore hold that Centocor has failed to prove that Abbott (BASF) suppressed or concealed.

Additional observation

In 1957, the CCPA stated:

> The issue here, however, is not whether Bailey has presented a perfect case, but whether he has presented a sufficient one.

Walker v. Bailey, 44 CCPA 998, 1005, 245 F.2d 486, 491 (CCPA 1957).

Our view of the arguments leads us to a conclusion that in many respects Centocor comes close to demanding a perfect case from Abbott. If Abbott's case had been perfect, Centocor would have settled and this case would not be before us. While not perfect, we hold that Abbott's case is sufficient and that is all that is required.

E. Order

Upon consideration of Abbott Motion 7, Centocor Opposition 7 and Abbott Reply 7, and for the reasons given, it is

ORDERED that Abbott Motion 7 is granted.

FURTHER ORDERED that Abbott has established an actual reduction to practice of the subject matter of the Count prior to any date offered by Centocor for its presumed actual reduction to practice.

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(cc via electronic mail)

Counsel for Centocor, Inc.,
an affiliate of Johnson & Johnson:

Barry E. Bretschneider, Esq.
Peter J. Davis, Esq.
MORRISON & FOERSTER LLP
1650 Tysons Boulevard, Suite 400
McLean, VA 22102

Tel: 703-760-7743 (Bretschneider direct)
Tel: 703-760-7748 or 202-887-1597 (Davis direct)
Fax: 703-760-7777
Email: bbretschneider@mofo.com
Email: pdavis@mofo.com

Counsel for Abbott GmbH & Co., KG:

John T. Callahan, Esq.
William J. Simmons, Esq.
SUGHRUE MION, PLLC
2100 Pennsylvania Avenue, Suite 800
Washington, D.C. 20037-3202

Tel: 202-293-7060 (main)
Tel: 202-663-7387 (Callahan direct)
Tel: 202-663-7950 (Simmons direct)
Fax: 202-293-7860
Email: jcallahan@sughrue.com
Email: wsimmons@sughrue.com